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BEHAVIORAL DISTURBANCES INDUCED BY NEONATAL THYROID HORMONE STIMULATION IN RATS

by

Per-Olow Sjödén

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Abstract

Deviations from a normal state of thyroid gland functioning during an early postnatal period result in permanent disturbances of brain, behavior and learning in man and animal. Neonatal thyroid-hormone stimulation is shown to produce behavioral hyperactivity in adult rats, due partly to an increased responsiveness to novel stimuli, and partly to a slower rate of habituation. Learning-effects of the early hormone-insult are demonstrated and shown to depend on learning test "complexity". Provision of an enriched pre-weaning environment counteracted behavioral hyperactivity and some learning-effects, whereas post-weaning enriched rearing conditions were less effective in this respect. A revised model for the understanding of behavioral changes after neonatal thyroid-hormone stimulation in rats is presented, based on findings in reviewed background literature and on experimental results on thyroid hormone - rearing conditions interactions. The neonatally thyroid-hormone-treated rat is suggested as a model for neonatal Graves' disease.

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The present dissertation is based on the following studies which will be referred to by their Roman numerals (see below).

I. Sjödén, P.O. & Söderberg, U. Effects of neonatal thyroxine stimulation on adult open-field behavior and thyroid activity in rats. Physiological Psychology, 4, 50-56, 1976a.

II. Sjödén, P.O. & Söderberg, U. Effects of neonatal thyroid hormone stimulation and differential preweaning rearing on open-field behavior in rats. Developmental Psychobiology, 9, 413-424, 1976b.

III. Sjödén, P.O. Effects of neonatal thyroid hormone stimulation and differential preweaning rearing on spatial discrimination learning in rats. Physiological Psychology, 4, 515-520, 1976c.

IV. Sjödén, P.O. & Lindqvist, M. Behavioral effects of neonatal thyroid hormones and differential postweaning rearing in rats. Developmental Psychobiology, submitted for publication.

SOME ABBREVIATIONS

T_3 = tri-iodothyronine

T_4 = thyroxine

neo-T_3/T_4 = stimulated neonatally with either T_3 or T_4

neo-T_3+T_4 = stimulated neonatally with a mixture of T_3 and T_4

T = neonatally thyroid-hormone treated group

C = control (saline) group

E = enriched rearing environment

I = impoverished rearing environment

Combinations of these, e.g. TI, CI, TE, and CE can be understood from the above list.

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1. INTRODUCTION

A multitude of factors are known to influence the development and adult functioning of brain and behavior in animals and man. Among these, hormones (Beach, 1975; Ford, 1971) and experiential factors (Moltz, 1971; Sterman, McGinty & Adinolfi, 1971) have been subjected to extensive research for several decades. Although most work has been concerned with the influence of either hormones or experience, some recent efforts have been made to study their synergistic or contradictory effects. Particularly, the question has been raised whether or not the long-term behavioral and learning effects of neonatal hormone-disturbances can be counteracted by environmental stimulation (Walsh & Greenough, 1976). The present thesis has two major aims: (1) To investigate some changes of behavioral activity and learning, alluded to in the existing literature, resulting from neonatal thyroid hormone disturbance in rats, (2) To further develop the line of research concerned with the combined or contradictory influences of thyroid hormones and experience on adult behavior and learning.

1.1. Hormonal factors

The thyroid gland was one of the first endocrine organs which was known with respect to general anatomy as well as to functioning (Tausk, 1975). Thus, already during the late 1800s, it was shown that thyroid deprivation leads to a clinical picture in man, which became known as myxedema, and that the development of this syndrome could be prevented by thyroid grafts or injections of thyroid extracts. The link between thyroid functioning and effects on the nervous system and behavior was established in 1888, in a report from the Clinical Society of London (Hökfelt & Dymling, 1973). Since then, an extensive literature concerned with the relationship between thyroid hormones and brain/behavior has developed (e.g. Reiss, 1958).

A lack of thyroid hormones in adult humans gives rise to a condition characterized by slow bodily motion, slow pulse and intestinal activity and a low body temperature. Also, apathy and a low degree of mental function, accompanied by slow speech and thought are often observed (Lewis, 1973). In contrast, a hyperactive thyroid gland gives rise to a clinical picture with excessive sweating, heat and weight loss, although many patients report a ravenous appetite. Other symptoms are trembling of the hands and muscle weakness. Both of these syndromes can be attributed

to the metabolic disturbances caused by the lack/excess of hormones; and both can be corrected by procedures aimed at adjusting the level of thyroid hormones to meet the current needs of the body tissues. In immature organisms, animals as well as man, a disturbance of the thyroid system during important developmental periods has more profound and partly different effects. In addition to an impairment of body growth and development, a lack of thyroid hormones gives rise to the well-known clinical entity of cretinism, characterized by a distorted facial appearance, a delayed skeletal age and a stunted development of mental and motoric landmarks. When left untreated, neonatal hypothyroidism (underfunction) results in irreversible damage to the nervous system, rendering the cretin mentally deficient (Hökfelt & Dymling, 1973). When occurring after two years of age, hypothyroidism in humans has little or no irreversible effects on mental functions (Smith, Blizzard & Wilkins, 1957). The limitations of replacement therapy for this condition are illustrated by the fact that intellectual deficits can be expected unless such therapy is implemented in humans before the age of three months (e.g. Klein, Meltzer & Kenny, 1972) or before 24 days of age in the rat (Eayrs, 1966). Even then, some infants may fail to respond (Eayrs, 1966; Klein, Meltzer & Kenny, 1972) and there is a large variation in the response to replacement therapy (ibid.). As a consequence of these observations, the possibility of a prenatal damage to the central nervous system (CNS) due to lack of thyroid hormones has been suggested (Eayrs, 1966). The latter possibility cannot be excluded since there is as yet not enough evidence for a placental transfer of sufficient amounts of thyroid hormones to compensate for a deficient thyroid activity in the fetus (Goslings, 1975; Greenberg, Najjar & Blizzard, 1974). Thus, there seems to be unequivocal evidence that the thyroid hormones excert different functions during different stages of development. Also, pre- as well as postnatally occurring deviations from a euthyroid state will lead to profound developmental disturbances. In the present thesis, manipulations of thyroid hormone levels will be restricted to the immediate postnatal period.

Whereas the consequences of a deficient activity of the thyroid gland are relatively well-known in immature as well as in adult organisms, the consequences of an excessive thyroid gland activity have received comparatively little attention. This is true especially for the immature organism and even more so when it comes to the long-term effects of neonatal hyperthyroidism (over-function) (Ford, 1971). Thus, neither the causal factors nor the long-term effects of neonatal hyperthyroidism are

fully known in man. Furthermore, the long-term behavioral and intellectual effects of an excessive neonatal thyroid hormone stimulation in children have only recently been investigated (Hollingsworth & Mabry, 1976; Wilroy & Etteldorf, 1971). Such effects are to be expected from the well-documented influence of neonatal thyroid hormone excess on brain development in animals (see Sections 2.1.1 and 2.1.2 below). In view of this lack of information concerning the long-term behavioral and learning effects of neonatal hyperthyroidism, the present work will be considered with this topic, using rat subjects. In particular, the rate of behavioral activity (Section 2.2.2) and learning (Section 2.2.3) will be investigated in adult rats, exposed to excessive amounts of thyroid hormones during the early neonatal period. An attempt will be made to develop an animal model of the disorder Neonatal Graves' Disease (neonatal thyrotoxicosis) (Section 6.1) and the model will be scrutinized with respect to fulfillment of criteria which can be reasonably expected to apply to such a model (Section 6.2).

1.2. Experiential factors

To-day, the assertion that the environment, and, particularly, the organism's interaction with it, play important roles in behavioral, intellectual and emotional development has become almost a truism. Also, many experimental investigations are concerned with the effects of various early environments on the subsequent behavioral and learning abilities of animals. Thus, it comes as no surprise that behavioral and learning differences can be effected by rearing animals in environments of varying complexity (Gluck & Harlow, 1971; Rosenzweig, Bennett & Diamond, 1971). This interest in environmental effects was greatly inspired by Hebb's (1949) experiments and proposals concerning the role of early experience in particular, in laying the foundation for later behavior and learning.

Experiential modification of brain characteristics has received less interest than has alterations of behavior and learning. Apart from scattered attempts during the 18th and 19th centuries (Rosenzweig, 1971) to show alterations of gross anatomical brain characteristics, no investigations of this matter were seriously undertaken until the 1950s. Since then, a number of brain characteristics, ranging from cortical weight and thickness (Rosenzweig, 1971) to the number of cortical synaptic connections (Greenough, 1975) have been shown to be sensitive to environmental conditions during early periods, at least in animals.

Although no unanimous opinion prevails as to the optimal developmental period for affecting such changes (Cummins, Walsh, Budtz-Olsen, Konstantinos & Horsfall, 1973; Riege, 1971; Rosenzweig, Bennett & Krech, 1964; Walsh & Cummins, 1975), most workers seem to agree that the early periods of an organism's life are "critical" (Greenough, 1975) or "sensitive" (Hinde, 1970) in this respect. In the present work, manipulations of the complexity of the rearing environment will be performed both during the pre- (Studies II-III) and post-weaning periods (Study IV) in rats. The environmental manipulations will follow the general format employed by the Rosenzweig group (e.g. Rosenzweig, Bennett & Diamond, 1972), although certain modifications were considered necessary since manipulations were also carried out during the pre-weaning period, and Rosenzweig has limited himself to dealing with the post-weaning period.

A related area of investigation, which has been initiated only very recently, is that of the effects of environmental-experiential influences in animal populations which have been in some way disadvantaged (Walsh & Greenough, 1976). Thus, the possibility of ameliorating the behavioral and neural effects of early brain damage, malnutrition, hormonal dysfunctions and social isolation, by providing animals with specific experiences has been investigated, Since the neural and behavioral effects of early brain insults on the one hand, and environmental enrichment on the other, are in many instances opposite to each other, such "therapeutic" effects of environmental enrichment can be reasonably expected (Walsh & Cummins, 1976b). The present work has as one additional aim to investigate the possibility of "normalizing" behavioral and learning disturbances resulting from neonatal thyroid hormone excess by environmental enrichment during the pre- and postweaning periods in rats.

Before going into the experimental studies (Section 5), first a summary of relevant background findings.

2. EFFECTS OF NEONATAL T_3- AND T_4-ADMINISTRATION

The short- and long-term effects in animals of a neonatal treatment with thyroid hormones have been subjected to several reviews (Eayrs, 1964b, 1968, 1971; Ford, 1968; Schapiro, 1971a, b). Considerable differences exist between the temporary and more persistent effects of neonatal thyroxine (T_4) or tri-iodothyronine (T_3) (neo-T_3/T_4)-treatment. For this reason, those arising before and after weaning (usually Day 21-23 in rats) will be considered separately. A summary of the effects induced during the periods before and after weaning is particularly pertinent to the present thesis, since manipulations of the rearing environment are performed prior to weaning in Studies I-III, and after weaning in Study IV. Differential effects of environmental manipulations in neo-T_3/T_4 rats during the pre- and post-weaning periods could presumably be understood in terms of the alterations induced by neo-T_3/T_4-treatment in the two phases of development (see Section 5.4.6).

2.1. Pre-weaning effects

Regardless of the specific variables monitored after neo-T_3/T_4-stimulation, a consistent picture of an advanced maturation emerges in the available literature. This holds for anatomical characteristics such as head length, external ears, eruption of the incisor teeth, opening of the eyes and skeletal age (e.g. Best & Duncan, 1969; Chen & Fuller, 1975; Davenport & Gonzalez, 1973; Davenport, Hagquist & Hennies, 1975; Eayrs, 1964a; Hoskins, 1927; Khamsi & Eayrs, 1966; Pelt, 1972; Rastogi & Singhal, 1976a, b; Schapiro, 1966, 1968; Weichsel, 1974). In contrast to this advancement of differentiation, growth processes have been reported to be severaly impaired in neo-T_3/T_4 animals. This has been manifested primarily as a reduction of bodily growth rate (e.g. Bakke, Lawrence & Wilber, 1974; Best & Duncan, 1969; Davenport & Gonzalez, 1973; Eayrs, 1964a; Eayrs & Holmes, 1962/63, 1964; Pelt, 1972, Salas, Díaz & Cintra, 1976; Schapiro, 1966, 1968; Schreiber & Kmentová, 1965/66). In those studies where body weight has been monitored during the adult period, the thyroid hormone-treated groups show a consistently lower body weight than controls.

Specific bodily organs have also been studied and the general pattern is that of lower organ weights, in some studies comparable to the reduction of body weight, and in others more severe for specific organs (primarily endocrine). Among the organs studied, the brain (Balázs,

Kovács, Cocks, Johnson & Eayrs, 1971; Chen & Fuller, 1975; Davenport & Gonzalez, 1973; Eayrs, 1964a; Kovács, 1973; Nicholson & Altman, 1972a; Pascual-Leone, Garcia, Hervás & deEscobar, 1976; Pelt, 1972), the cerebellum (Balázs, Kovács, Cocks, Johnson & Eayrs, 1971; Kovács, 1973; Weichsel, 1974), the thyroid (Azizi, Vagenakis, Bollinger, Reichlin, Braverman & Ingbar, 1974; Bakke & Lawrence, 1966, 1968; Bakke, Lawrence & Robinson, 1972; Bakke, Lawrence, Bennett & Robinson, 1975; Best & Duncan, 1969; Eayrs & Holmes, 1964; Gellert, Bakke & Lawrence, 1971), the adrenals (Bakke, Lawrence & Wilber, 1974; Bakke, Lawrence, Bennett & Robinson, 1975; Meserve & Leathem, 1974), the pituitary (Bakke & Lawrence, 1966; Bakke, Lawrence & Robinson, 1972; Bakke, Lawrence & Wilber, 1974), the testes (Bakke, Lawrence & Wilber, 1974; Bakke, Lawrence, Bennett & Robinson, 1975; Pelt, 1972), the ventral prostate (Bakke, Lawrence & Wilber, 1974), and liver and kidney (Pascual-Leone, Garcia, Hervás & deEscobar, 1976) have all been observed to weigh less in hormone-treated rats than in controls. Some of these effects also persist into the adult age.

Growth can be defined as a permanent increase of body mass, and differentiation refers to a progressive diversification of cell structure and function leading to morphogenesis (Greenberg, Najjar & Blizzard, 1974). Using these definitions, the effects of a neonatal administration of thyroid hormones on anatomical features may be characterized as an increase in the rate of differentiation and a concomitant reduction of growth rate. The latter is particularly true for high doses of thyroid hormone.

The reduction of growth rate has been proposed to result from a damage to the acidophile cells of the pituitary, thought to be involved in growth hormone production (Eayrs & Holmes, 1962/63, 1964). In fact, a lower pituitary growth hormone content has been reported in neo-T_4 rats (Pascual-Leone, Garcia, Hervás & deEscobar, 1976). However, it is unclear if this reduction is an effect of the secondary hypothyroidism produced by neonatal T_3/T_4-treatment (Section 2.2.1), or if it involves a direct derangement of hypothalamic-pituitary function (ibid.). Replacement therapy with growth hormone has not yet been successful in reversing the lower rate of body weight gain (deRaveglia, Gómez & Ghittoni, 1973; Eayrs & Holmes, 1964; Eayrs, 1964a). Substitution with thyroid hormones has likewise failed to alter rate of bodily growth (Best & Duncan, 1969; Schreiber & Kmentová, 1965/66). There seems to be considerable support for the opinion that the reduction of body weight

and growth rate is due to an accelerated maturation speed of the neuroendocrine system controlling the slowing and eventual cessation of growth processes (Best & Duncan, 1969; Chen & Fuller, 1975). Thus, a more rapid functional differentiation may imply a reduction in the length of the period of growth.

It is of considerable interest for the present work that the development of a number of indices of CNS-functioning has been reported to be considerably advanced by neo-T_3/T_4-treatment. Thus, there is a premature development of the CNS as assessed by neurochemical, neuroanatomical, neurophysiological, and behavioral indices in neo-T_3/T_4 rats. An overview of the literature on these four points and with respect to endocrine parameters follows below.

2.1.1. Neurochemical/neuroanatomical. Since most of the studies concerned with microanatomical development of the CNS have utilized indirect biochemical methods, they are both included under the same heading.

It is well-known that excess thyroid hormone increases the oxygen consumption of immature brains (Greenberg, Najjar & Blizzard, 1974). This phenomenon is presumably related to the active growth and development of the brain during the early postnatal period in rats (Bekoff & Fox, 1972) as well as in man (Dobbing, 1975). In immature rats, there is very little transport of cerebral glucose and adult values are not reached until 20 days of age. In neo-T_4 rats, however, an adult pattern of cerebral glucose transport is reached already by Day 15 (Moore, Lione & Regen, 1973).

A compression of the ontogenetic development of the pattern of brain enzyme systems, shown by an early appearance of peak and drop to characteristic adult levels, has been reported in neo-T_4 rats (Anderson & Schanberg, 1975). Neo-T_4-treatment has been shown to accelerate the amino acid incorporation into brain protein in the early (10-15 days) period after birth, which coincides with the period of T_4-action on brain maturation (Macho, Štrbák & Hromadová, 1972). Kovács (1973) has reported an earlier peak and slope of protein synthesis in the hypothalamus of neo-T_3 animals as compared to controls. This alteration of hypothalamic development may indicate that ramifying consequences to several endocrine systems as a result of neo-T_3-treatment are to be expected at a later age. Other studies (Section 2.2.1) confirm this expectation.

The rate of active myelinization has been repeatedly shown to be affected by neonatal thyroid hormones. Thus, a higher content of cholesterol in the brain (Phelps & Leathem, 1976; Schapiro, 1966, 1968) in rats

aged between 6 and 20 days has been reported. Also, an increased cerebellar content of proteolipid protein by Day 10 (deRaveglia, Gómez & Ghittoni, 1973), an accelerated development of brain fatty acid hydroxylase activity, with the peak shifted to an earlier age (Murad, Strycharz & Kishimoto, 1976), and an accelerated rate of incorporation of P^{32} into brain lipids (Adreleanu, Stefan & Sterescu, 1971) have been reported after neo-T_3/T_4-treatment. All these reflect various aspects of an advanced myelinization process. Higher levels of brain cholesterol, cerebrosides and sulfatides and an adult-like composition of myelin lipids were present in neo-T_4 rats at 10 days of age as contrasted to Day 20 in normal rats (Dalal, Valcana, Timiras & Einstein, 1971).

The ontogeny of the dendritic spines of cortical pyramidal cells has been shown to be advanced after neo-T_4-treatment (Eayrs, 1964b; Schapiro 1968). Recently, Salas, Díaz and Cintra (1976) have demonstrated that neo-T_4-treatment results in an initial increase in the number of spine processes of the cortical pyramidal cells. By Day 20, however, a significant decrease in the number of spines occurred. Also, the development of the mechanism of conversion of glucose-carbon to amino acids has been reported displaced to an earlier age by neo-T_3-treatment (Cocks, Balázs, Johnson & Eayrs, 1970). This may be one of the major biochemical mechanisms underlying dendrite- and nerve terminal-formation. Thus, the data on dendritic spine development indicate that there is an accelerated cell differentiation after neonatal hyperthyroidism.

Another reflection of the accelerated cell differentiation after neo-T_3/T_4-treatment is an advanced cerebellar synaptogenesis, during the first two weeks after stimulation. By Day 21, however, the number of synapses is progressively reduced below control values (Nicholson & Altman, 1972b) until the ultimate result of the thyroid hormone-treatment is a reduction even in the final total number of synapses. It has also been shown that neo-T_4-administration decreases significantly the DNA content of both the cerebrum and the cerebellum (ibid.). This indicates a deficiency in the number of nerve cells formed postnatally. Balázs, Kovács, Cocks, Johnson and Eayrs (1971) have reported a permanent deficit in the total number of cells both in the cerebrum and the cerebellum after neo-T_3-treatment. No effects have been observed on cell size (ibid., Kovács, 1973; Nicholson & Altman, 1972a). As mentioned earlier, there is an advanced cell differentiation after neo-T_3/T_4-stimulation. This may be the mechanism behind the reported reduction of postnatally formed nerve cells. Thus, the cerebellum develops more

rapidly in neo-T_3 rats than in controls, which may lead to a premature termination of cell multiplication (Nicholson & Altman, 1972a). An increase of cell proliferation, as measured by DNA content in the cerebellum, is evident during the first week, followed by a decrease by Day 12 (Gourdon, Clos, Coste, Dainat & Legrand, 1973; Weichsel, 1974).

Some recent studies have been directed at mapping out the effects of neo-T_3/T_4-stimulation on the putative neurotransmitter systems in rats. In 1968, it was shown by Schapiro that the activity of acetylcholinesterase (AChE) was increased in the cortex and hypothalamus of neo-T_4 rats as compared to controls. Two studies by Rastogi and Singhal (1976a, b) have shown that neonatal thyroid hormones excert an important influence upon the metabolism of neurotransmitters in the developing brain. After having shown an increased behavioral activity after neo-T_3-stimulation (Rastogi & Singhal, 1976a) these authors advanced the hypothesis that the increase was caused by an increased activity of catecholaminergic neurons. They have later reported that neo-T_3-treatment gives rise to an increased synthesis and utilization of catecholamines and of 5-hydroxytryptamine in rats (Rastogi & Singhal, 1976a, b).

In conclusion. Several indices of CNS-development show an earlier appearance of an adult pattern in neo-T_3/T_4 rats. Also, for the development of dendritic spines and neural synapses, neo-T_3/T_4 animals show a reduced value around Day 20, even below that of controls.

2.1.2. Neurophysiological. A more rapid appearance of an adult EEG pattern and earlier changes of amplitude and frequency in response to external stimuli after neo-T_4-treatment was shown by Schapiro (1968; Schapiro & Norman, 1967). Most investigations have been concerned with the maturation of cortical evoked responses. Thus, recording from the sensory motor cortex, an accelerated development of evoked responses to sciatic nerve, auditory and visual stimulation was shown in neo-T_4 rats (Schapiro, Salas & Vukovich, 1970). Also, an earlier appearance of the cortical responsiveness to auditory stimuli and an advanced organization of visual and sensorimotor responses have been shown after neo-T_4-stimulation (Salas & Schapiro, 1970). Recently, Salas, Díaz and Cintra (1976) reported an advanced development (by 2-3 days) of evoked cortical responses before Day 20 in neo-T_4 rats. After Day 20, however, a retardation of the development occurred. Thus, as was true for cerebellar synaptogenesis and cell formation, and for cortical pyramidal cell spine development (Section 2.1.1), there is evidence of an initial acceleration of the development, followed by a later retardation.

In mice, the development of audiogenic seizure responsiveness has been shown advanced by 3-4 days in neonatal hyperthyroidism (Hamburgh & Vicari, 1957).

2.1.3. Endocrinological. Few investigations have been concerned with the short-term effects of neo-T_3/T_4-treatment on endocrine function. However, an accelerated development of the pituitary-adrenal response to stress after neo-T_3-treatment of rats has been reported (Meserve & Leathem, 1974; Schapiro, 1968; Schapiro & Norman, 1967).

2.1.4. Behavioral. The appearance of simple, discrete reflex patterns has been repeatedly proved to be advanced in neo-T_3/T_4 animals. Thus, the startle reflex response to sudden loud sounds has been shown advanced in mice (Chen & Fuller, 1975; Hamburgh, 1958; Hamburgh & Vicari, 1957) and in rats (Eayrs, 1966; Khamsi & Eayrs, 1966; Rastogi & Singhal, 1976b; Schapiro, 1968). Also, the righting reflex (Davenport & Gonzalez, 1973; Eayrs, 1964a; Khamsi & Eayrs, 1966; Pelt, 1972; Rastogi & Singhal, 1976b), the air-righting reflex (Chen & Fuller, 1975; Davenport, Hagquist & Hennies, 1975) and the placing reflex (Eayrs, 1964a; Khamsi & Eayrs, 1966; Pelt, 1972; Rastogi & Singhal, 1976b) have been shown advanced by 1-2 days in neo-T_3/T_4 rodents. In neonatally T_3/T_4-treated mice (Hamburgh & Vicari, 1957; Murphy & Nagy, 1976b) and rats (Anderson & Schanberg, 1975; Davenport & Gonzalez, 1973; Davenport, Hagquist & Hennies, 1975; Schapiro, Salas & Vukovich, 1970) a consistently earlier appearance of the characteristic adult pattern of swimming has been reported. With respect to the grasp-hold reflex, variable results have been forthcoming. Thus, no effects were found in some studies (Chen & Fuller, 1975; Davenport, Hagquist & Hennies, 1975) and an accelerated development in at least one study (Davenport & Gonzalez, 1973). Due to the muscular tremor, regularly seen in neo-T_3/T_4-animals during the first days after the injection, reliable recordings of the grasp-hold reflex may be difficult to get, which may explain the divergent results.

Behavioral activity, measured either by unsystematic observations, stabilimeter or open-field tests, has been reported to be elevated in neo-T_3/T_4 rats (Eayrs, 1964a; Schapiro, 1966, 1968). Corroborative reports have been forthcoming successively (Davenport, Hagquist & Hennies, 1975; Rastogi & Singhal, 1976a, b; Weichsel, 1974). Using a standard open-field situation with rats aged 6-20 days, Chen and Fuller (1975) did not find any evidence of an elevated behavioral activity after neo-T_4-stimulation, nor did Pelt (1972) at 30 days of age in a residential-plus maze. These are apparently the only reports of negative findings.

A single injection of T_3 in golden hamsters on Day 3 after birth has been shown to cause an augmented open-field ambulation at Day 20 (Darling, 1966).

In normal rats and mice, there is a marked elevation of activity from Day 9 to Day 15 and a subsequent decline (Campbell & Mabry, 1972). In an attempt to investigate whether or not this peak can be displaced in time by neo-T_3-treatment, Davenport, Hagquist and Hennies (1975) tested rats in stabilimeter cages between Days 7 and 20. However, they found no displacement of the activity peak. Also, using the identical experimental set-up with neo-T_4 mice, Murphy and Nagy (1976a, c) failed to find an earlier peak. However, by administering the anti-cholinergic drug scopolamine, they were able to show an activity increase in response to the drug 2 days earlier in their experimental animals than in their controls. This finding supports the suggestion that neo-T_4-treatment advances cholinergic inhibitory functioning in mice (cf. Section 2.1.1).

An early report of a superior acquisition of a one-way avoidance response in neo-T_4 rats (Schapiro & Norman, 1967) at Days 16-18 after birth, has been recently supported (Stone & Greenough, 1975). However, two-way active avoidance responding at 19-20 days was not superior in neo-T_4 rats (Davenport & Gonzalez, 1973). With respect to passive avoidance responding, neo-T_4 animals have been shown to be inferior to controls at 16-18 days (Stone & Greenough, 1975), but no significant effects at 19-20 days have also been found (Davenport & Gonzalez, 1973). A somewhat more complicated escape-test, utilizing a geotactic (up-down on an inclined plane) discrimination (Stone & Greenough, 1975) failed to produce any evidence of an influence of neo-T_4-treatment.

Recently (Murphy & Nagy, 1976b), some T_4-treated (T) and some saline-injected (S) mice were trained to escape shock in a straight runway (TC and SC groups) and some were trained to escape shock in a T-maze (TE and SE groups) at 7, 9, 11, and 13 days of age. The neo-T_4 animals showed faster running speeds in the straight alley. At a retention test 24 hrs after the original training, only the TE group showed a superior retention on Days 10-12, but an inferior retention on Day 14. The authors conclude that neo-T_4-treatment advanced the retention ability of the treated animals. Apart from that, the latter study again illustrates the pattern of an early stimulation of development, followed by a later retardation, as was already described for some neurochemical/neuroanatomical and neurophysiological parameters (Sections 2.1.1 and 2.1.2).

Conclusion. During the pre-weaning period, the neo-T_3/T_4 rat is pri-

marily characterized by an advanced development of anatomical, behavioral and CNS features. Towards Day 20, however, there are signs of retardation of developmental processes to a level even below that of the controls. Many developmental patterns of CNS-functioning are compressed into a shorter time interval than for normal rats. There are indications of a faster learning of simple tasks in neo-T_3/T_4 rats as compared to controls. This pattern of an advanced pre-weaning development of CNS-functioning, followed by a later retardation will be used as a cornerstone in the theoretical model developed below (Sections 5.4.5 and 5.4.6).

2.2. Post-weaning effects

As mentioned above, there is considerable evidence that a neonatal exposure to T_3 and T_4 results in permanently lower body and organ weights also during the post-weaning and adult periods. The summary below will deal with endocrine and behavioral activity and learning effects. No studies of CNS-characteristics have been performed in adolescent and adult neo-T_3/T_4 rats.

2.2.1. Endocrinological. The exposure of newborn female rats to androgens during a critical formative period has been shown to result in permanent alterations of the hypothalamic centers regulating pituitary gonadotropin secretion (e.g. Harris, 1964). Thus, an overdose of gonadal hormone during the period when the major CNS and endocrine controls over endocrine function are established, results in a permanent "re-setting" of the gonadal hormone system. Analogously, it has been hypothesized that an overdose of thyroid hormone would permanently "set" the thyroid system at a lower than normal level (Bakke & Lawrence, 1966; Eayrs & Holmes, 1964). This would then be reflected in terms of a hypothyroid state in the adult animal.

Among the first studies reported, only small defects of thyroid function were noted (Best & Duncan, 1969; Eayrs & Holmes, 1964; Schreiber & Kmentová, 1965/66; Swanson & van der Werff ten Bosch, 1965). Since then, a great number of studies have contributed to the understanding of the so-called "neo-T_4-syndrome" (Bakke, Lawrence & Wilber, 1974; Bakke, Lawrence, Bennett & Robinson, 1975), which is defined by the following characteristics: (1) lower thyroid and pituitary weights, often disproportionately lower than the body weight (Bakke & Lawrence, 1966), (2) a lower I^{131} uptake of the thyroid (Azizi, Vagenakis, Bollinger, Reichlin, Braverman & Ingbar, 1974), (3) a reduced serum PBI level (Gellert, Bakke & Lawrence, 1971), (4) lower circulating levels of free T_3 and T_4 in

plasma (Gellert, Bakke & Lawrence, 1971; Pascual-Leone, Gomez, Hervás & deEscobar, 1976), (5) lower total pituitary thyroid stimulating hormone (thyrotropin) (TSH) (Bakke & Lawrence, 1966; Gellert, Bakke & Lawrence, 1971) and growth hormone contents (Pascual-Leone, Garcia, Hervás & deEscobar, 1976), (6) lower circulating TSH levels (Bakke, Lawrence & Wilber, 1974), (7) an elevated stalk-median eminence content of TSH (Bakke & Lawrence, 1966), (8) an increase of thyrotropin releasing hormone (TRH) in the hypothalamus (Bakke, Lawrence & Wilber, 1974), (9) a lesser goitrogenic enlargement of the thyroid after propylthiouracil (PTU, an antithyroid drug) (Bakke & Lawrence, 1966; Phelps & Leathem, 1976) and (10) a lesser increase of serum TSH, a lesser depletion of pituitary TSH (Bakke & Lawrence, 1966) and a reduced pituitary gland enlargement at PTU challenge (Phelps & Leathem, 1976).

Thus, it has been concluded that rats with the neo-T_4 syndrome have a subnormal pituitary responsiveness to TRH, possibly associated with a chronic deficiency of TRH secretion (Bakke, Lawrence & Wilber, 1974). In addition, neo-T_4 rats are hypersensitive to feedback regulation by T_4 (Bakke, Lawrence, Bennett & Robinson, 1975), much in the same way as are animals with bilateral anterior hypothalamic lesions of the thyrotropic area. Thus, there seems to be a lowering of the "set point" of the hypothalamic-pituitary regulation of the thyroid axis in adult neo-T_4 animals.

A suspicion was expressed early (Eayrs & Holmes, 1962/63, 1964) that regulation of gonadal hormones was also deranged by neo-T_3/T_4-exposure. In fact, presently available evidence shows a retarded vaginal opening and first estrus (Bakke, Gellert & Lawrence, 1969; Gellert, Bakke & Lawrence, 1971), prolonged estrus cycles (Bakke, Lawrence & Robinson, 1972) and reduced ovarian (Bakke, Lawrence & Robinson, 1972), reduced testes and ventral prostate weights (Bakke, Lawrence & Wilber, 1974). Also, an impaired fertility in neo-T_4 males and females (Bakke & Lawrence, 1968; Best & Duncan, 1969), sometimes associated with a high mortality in the offspring (Bakke, Gellert & Lawrence, 1969) has been reported. It thus seems likely that neo-T_4-treatment permanently alters some hypothalamic mechanism concerned with both thyrotropic and gonadotropic secretion.

2.2.2. Behavioral activity. In view of the findings of a low but consistent degree of secondary hypothyroidism in neo-T_3/T_4 animals (Section 2.2.1) an accompanying low rate of behavioral activity would be expected. This is so, since the traditional view has been that hypothyroidism, at least if induced during the adult period in rats, is accompanied by low

motor activity (Brody, 1941; Hall & Lindsay, 1938; Richter, 1933; Stern, 1970). However, the few reports on activity in neo-T_3/T_4 rats point in the opposite direction, i.e. a higher rate of behavioral activity.

Thus, there are a few scattered reports indicating long-term persistence of the behavioral hyperactivity seen in pre-weaning neo-T_3/T_4 rats (Section 2.1.4). Schapiro (1968) found neo-T_4 animals to show a higher activity in an open-field test at 30-40 days of age. Also, Lât and Gollovà-Hémon (1969) reported that neo-T_4-injections caused an increased rate of rearing behavior at 40 days of age. Using a residential-plus maze, Pelt (1972) found a higher activity in two separate groups of neo-T_3-treated rats at three months of age. Also, Rastogi and Singhal (1976a) have shown that neonatal T_3-treatment causes an increased locomotor activity in an automated activity meter in rats aged 14-105 days. Davenport and Gonzalez (1973) found that low-dose neo-T_4 rats did not show an elevated activity in a running wheel test at approximately 140 days of age. However, the test lasted only 15 days, which may have been too short for reliable differences to develop (Finger, 1972). Considering the above data from a methodological point, it is evident that those workers who have tested adult (as opposed to adolescent) rats (with the exception of Rastogi and Singhal, 1976a) have not employed standard tests for the assessment of behavioral activity.

There is an apparent lack of reliable data on long-term effects on behavioral activity, although some indications of an elevation after neo-T_3/T_4-treatment have been found. The correlation of adult hypothyroidism with high locomotor activity squares very badly with the traditional view mentioned above. However, some workers have found that surgical thyroidectomy in adult rats causes high rates of rearing and locomotion in a two-compartment test (Dupont, Endröczi & Fortier, 1971), thus questioning the traditional view. Also, evidence has been forthcoming (e.g. Davenport, 1976; Pelt, 1972) that rats made hypothyroid during the neonatal period do indeed show an elevated rate of activity as adults.

In the present thesis, two problems concerned with behavioral activity will be attacked experimentally: (1) Can behavioral hyperactivity after neo-T_3+T_4-treatment be shown to be a replicable and permanent phenomenon? (Section 5.4.1); (2) If so, how can the behavioral hyperactivity be accounted for? (Section 5.4.2).

2.2.3. Learning. As has already been reviewed, there is a marked acceleration of CNS- and behavioral development in neo-T_3/T_4 rats (Sections

2.1.1, 2.1.2, and 2.1.4). Also, an enhanced pre-weaning performance in the one-way active avoidance test (Schapiro & Norman, 1967; Stone & Greenough, 1975) has been reported. On the other hand, the many detrimental effects of neo-T_3/T_4-treatment on CNS parameters (Sections 2.1.1 - 2.1.2) could presumably permanently compromize the ability of neo-T_3/T_4-animals to learn. In fact, most investigators have reported a deficient performance in a number of learning tests.

In 1964 (Eayrs, 1964a), it was shown that neo-T_3 rats committed significantly more errors than controls on a complex maze, the Hebb-Williams closed-field test (Hebb & Williams, 1946; Rabinovitch & Rosvold, 1951) at the age of 100 days. These results were later confirmed by Khamsi and Eayrs (1966). The performance of neo-T_4-animals at 35-45 days in the Lashley III maze and a Y-shaped water-maze (Schapiro, 1968) was also shown to be deficient. Using a modified Hebb-Williams maze, the symmetrical maze, Davenport and Gonzalez (1973) provided further evidence of an inferior performance at 70-85 and 180 days on the part of neo-T_4 rats. These authors (ibid.) also found that passive avoidance learning was deficient in rats 35-36 days of age. The results obtained with the symmetrical maze were later extended to neo-T_3 rats as well (Davenport, Hagquist & Hennies, 1975) in tests performed at 180 days of age. Recently, 40-day-old rats were shown to be inferior to controls on the Lashley III maze (Stone & Greenough, 1975). This effect was not altered by replacement therapy with T_4, given at the time of maze-testing, thus indicating that the slight hypothyroidism expected in these animals, did not contribute significantly to their learning deficiency. Employing two groups of neo-T_3-treated rats, Pelt (1972) was unable to find any learning deficiency in the Hebb-Williams maze at 160 days of age.

It should be noted that most of the tests used to show learning deficiencies in neo-T_3/T_4 rats are of a rather complex nature. E.g. the Hebb-Williams and closed-field mazes are among the most complex tests for use with rodents. Thus, it is an open question whether or not less complex tests will evidence an identical pattern of learning deficits. Also, if behavioral hyperactivity in neo-T_3/T_4 rats in some way influences their deficient learning, it can be expected that some tests are more "sensitive" to this influence than others. The question of whether or not neo-T_3+T_4-induced learning deficits are consistent across learning tests will be investigated experimentally in the present work (Section 5.4.3). Also, a model proposed by Schapiro (1971a) to account for the learning deficits in neo-T_3/T_4 rats will be tested and further developed. (Section 5.4.6).

Conclusion. The adolescent and adult neo-T_3/T_4 rat is characterized by a slight secondary hypothyroidism and a disturbance of gonadal function, due to interference with hypothalamic-pituitary mechanisms. There are indications of a behavioral hyperactivity in a few reports. Also, deficiencies of learning have been reported as early as 35 days of age.

3. EFFECTS OF DIFFERENTIAL REARING ENVIRONMENTS

Some reviews concerned with the influence of the early environment on several characteristics of animals are available. Most of these have considered mainly direct neural effects (Greenough, 1975; Rosenzweig, 1971; Rosenzweig, Bennett & Diamond, 1971, 1972), although behavioral and learning effects have at least been mentioned passingly. There are few reviews of the latter area (Gluck & Harlow, 1971; Harlow, Harlow, Schiltz & Mohr, 1971), perhaps due to the fact that the available literature is strikingly heterogenous with respect to findings as well as to conceptual and methodological considerations.

One difficult problem is that of a definition of the terms enriched and impoverished environments (Rosenzweig, 1971; Rosenzweig, Bennett & Diamond, 1972). The problem consist mainly of how to define an appropriate baseline for rearing environments. It is obvious that the standard laboratory environment has very few characteristics in common with the natural environment to which the various animal species have been adapted. Thus, during the pre-weaning period, the normal laboratory environment can be considered largely "overstimulating" as compared to the normal nesting environment of rats (Daly, 1973). After weaning, the laboratory conditions are clearly "understimulating". Efforts to "enrich" or "impoverish" laboratory conditions must be judged in this light, and not be considered in relation to the natural environment for a certain species, unless such environmental conditions have been studied (e.g. Rosenzweig, Bennett & Diamond,1972). In most studies reviewed below, only two types of environment have been included: impoverished (I) and enriched (E). In some, a third, baseline condition termed social control has been included. The most widely accepted solution to this problem is to consider impoverishment and enrichment as arbitrarily defined for each experiment. This may raise severe problems in certain contexts. For one of the main themes of the present thesis, that of "environmental therapy" for hormonally induced behavioral disturbances, it is necessary only to clarify whether a difference of complexity of the rearing environment between two conditions interacts with neo-T_3/T_4-treatment for certain behavioral variables (Sections 5.4.4 and 5.4.5).

In order to parallel the classification of effects of neo-T_3/T_4-treatment, the distinction between pre- and post-weaning effects will be upheld in the following section.

3.1. Effects of differential pre-weaning rearing

In spite of the fact that several workers have stressed the plasticity of the nervous system and its sensitivity to environmental stimulation during the pre-weaning period (Bekoff & Fox, 1972; Schapiro, 1971a), very few studies have included environmental manipulations during this period.

Malkasian and Diamond (1971) carried out what seems to be the first (and only) study of the effects of pre-weaning enriched (E) rearing on neuroanatomical development. They raised unifamily (UFE = one dam plus three pups), multifamily (MFE) and enriched-multifamily (EC-MFE) groups of rats between Days 6 and 30 and found no differences between the UFE and MFE conditions on brain morphology. However, the EC-MFE rats showed greater cortical depths at all ages studies (14-28 days), with the exception of the visual cortex at Day 14. Neuronal nuclear and perikaryon areas in the somatosensory and occipital cortices were also greater in EC-MFE rats at Day 28. A variety of pre-weaning stimulation has been shown to result in an increased number of dendritic spines of the cortical pyramidal cells and a higher number of functionally active neurons (Schapiro & Vukovich, 1970).

In the study by Malkasian and Diamond (1971), an effort was made to study the behavioral activity of the various groups in their respective environmental conditions. The enriched multifamily group explored their cages more than the non-enriched unifamily group. Smith (1972) found that pre-weaning I-rearing increased open-field ambulation between age 66 and 70 and between 92 and 96 days.

In an effort to delineate "crucial periods" for environmental enrichment-effects on adult learning, Forgays and Read (1962) included the pre-weaning period. They found that animals from the enriched condition made fewer errors than non-enriched on the Hebb-Williams maze at 123 days of age. Enriched environmental conditions from Day 1 to Day 21 have been shown to result in lower Hebb-Williams error scores (Denenberg, Woodcock & Rosenberg, 1968). The most recent study of pre-weaning E-effects on adult learning scores (Smith, 1972) provided no facilitating influence on Hebb-Williams performance. This contradicts previous findings in the Hebb-Williams maze, but the fact that Smith (1972) excluded retracing errors may have been of significance. This is so, since the pre-weaning impoverishment has been shown to result in increased behavioral activity (Smith, 1972; Woods, Ruckelshaus & Bowling, 1960; Table 1B).

Conclusion. Some tentative conclusions from pre-weaning differential

rearing studies may be drawn: an increased activity after I-rearing and a better learning performance after E-rearing have been found. The effects found on brain parameters are similar to those found during the post-weaning period (Section 3.2) and, in some cases, more powerful than the latter.

3.2. Effects of differential post-weaning rearing

Some of the first studies were concerned with the effects of formal training on cholinesterase (Che) and it was reported that such training increased total cortical ChE (Rosenzweig, Bennett & Diamond, 1971), as did E-rearing after weaning (Rosenzweig, Krech, Bennett & Zolman, 1962).

Increases of cortical acetylcholinesterase (AChE) (Rosenzweig, Krech, Bennett & Zolman, 1962) and of the RNA/DNA ratio and of total protein (Rosenzweig, Bennett & Diamond, 1971, 1972) have also been reported. These findings indicate a higher metabolic activity in neural tissues, possibly accounting for the increased brain and cortical weight (Ferchmin, Bennett & Rosenzweig, 1975; Rosenzweig, Krech, Bennett & Zolman, 1962), length (Walsh, Cummins & Budtz-Olsen, 1973) and thickness (depth) (Diamond, 1967; Diamond, Ingham, Johnson, Bennett & Rosenzweig, 1976) reported after enriched post-weaning rearing. Also, the number of glial cells (Rosenzweig, 1971; Walsh, Budtz-Olsen, Penny & Cummins, 1969) and glial cell ChE activity have been reported increased (Brown, 1971) as well as an increase of the neuronal nucleus and perikaryonal size (Diamond, 1967). All of the above effects show a certain amount of regional specificity, by being most pronounced in the occipital region. The subcortical regions have invariably shown a lower weight, width and length in E-animals (Walsh, Cummins, Budtz-Olsen & Torok, 1972), resulting in an increase of the cortical/subcortical weights as being one of the most sensitive indices of enrichment-effects. Dendritic arborization (Greenough, Yuwiler & Dollinger, 1973; Volkmar & Greenough, 1972) as well as the number of dendritic spines (Rosenzweig, 1971) have been shown to increase after post-weaning enrichment. Effects of enrichment have also been reported in the hippocampus (Rosenzweig, 1971; Walsh, Budtz-Olsen, Penny & Cummins, 1969), where the depth was reported to increase. However, contradictory findings (Diamond, Ingham, Johnson, Bennett & Rosenzweig, 1976) make these results equivocal.

The studies of behavioral activity after post-weaning E-rearing yield a thoroughly confusing picture. On the one hand, several studies have found an increase of activity after enrichment (Table 1A), others have

Table 1[a]

Listing of Studies on the Effects of Differential Post-Weaning Experiences on Behavioral Activity in Normal Rodents.

Reference	Treatment age(s)	Test + age(s)
A. Findings of an enhanced activity in enriched rodents.		
Stern, Winokur, Eisenstein, Taylor & Sly, 1960.	23-	Closed-field,58-65.
Duke & Seaman, 1964.	21 (?)-121	Open-field,122-136.
Luchins & Forgus, 1955.	18-70	Elevated maze + Y-maze,71.
Gill, Reid & Porter, 1966.	21-81	Open-field,90.
Lore & Levowitz, 1966.	25-65	Home-cage emergence, 86.
Schweikert & Collins, 1966.	25-115	Hebb-Williams maze, 75.
McCall, Lester & Dolan, 1969.	24-77,24-144	Open-field,78-90, 145-147.
Manosevitz,1970.	0-35 (mice)	Open-field,38.Running wheel 70-107.
Nielsen, 1970.	21-91 (?)	Closed-field,91. Preference test,100.
Nielsen, 1971.	21-81	Visual-tactual exploration,96,104.
Manosevitz & Montemayor, 1972.	0-38 (mice)	Open-field,41,60. Running wheel,66.
Manosevitz & Joel, 1973.	0-38 (mice)	Open-field,running wheel,38.
Morgan, 1973.	21-105 (social)	Emergence test,105.
Ferchmin, Bennett & Rosenzweig, 1975.	65-96	Greek cross,97.
Gardner, Boitano. Mancino, D`Amico & Gardner, 1975.	21-93 (perceptual)	Closed-field,93. Open-field,98.
Huck & Price, 1975.	25-97	Various.
Manosevitz & Pryor, 1975.	0-38 (mice,cage size)	Open-field,41.
Einon & Morgan, 1976.	17-50 (social)	Open-field,60.

a) The treatment age(s)-column also indicates other rodent species than rats and whether any particular type of enrichment was used.

Continued.

Table 1 continued

B. Findings of an enhanced activity in impoverished rodents.

Zimbardo & Montgomery, 1957.	21-46,21-71, 21-121	Y-maze,47, 72,122.
Ehrlich, 1959.	21-70	Y-maze, Dashiell maze,76-79.
Woods, 1959.	23-154	Closed-field, 156.
Woods, Ruckelshaus & Bowling, 1960.	21-175	Closed-field, 175-185.
Woods, Fiske & Ruckelshaus, 1961.	25-180	Hebb-Williams maze, 66,161.
Denenberg, Schell, Karas & Haltmeyer, 1966.	21-70	Open-field,75.
Lore & Levowitz, 1966.	25-65	"Forced exploration", 121.
Lore, 1968.	25-53	Novel cage,61,67.
Smith, 1972.	0-21,22-56	Open-field,66-70.
Levitsky & Barnes, 1972.	0-49	Open-field,126.
Morgan, 1973.	21-105 (social)	Shuttling behavior and activity,108-168.
Syme, 1973.	23-190	Open-field,190.
Einon & Morgan, 1976.	17-50 (social)	Open-field,habituation, 60.

C. Findings of no difference between enriched and impoverished rodents.

Forgays & Read, 1962.	0-109	Y-maze,114.
Denenberg & Morton 1962 a.	21-50	Open-field,180.
Moyer & Korn, 1965.	21-111	Open-field,111.
Brown, 1968.	20-100,60-100, 20-60	Hebb-Williams maze, 60.
McCall,Lester & Dolan, 1969.	24-77	Open-field,78-90.

reported an increase after impoverishment (Table 1B), and still others have observed no differences between E and I rats (Table 1C). To confuse the picture further, some studies have looked into the importance of social/non-social rearing, as being one of the major variables which usually differentiates post-weaning E from I conditions. From these studies, the conclusion emerges that social isolates have a tendency to run more (locomotion) (Morgan, 1973; Morgan, Einon & Nicholas, 1975) and to habituate their open-field activity slower than enriched animals (Einon & Morgan, 1976; Einon, Morgan & Sahakian, 1975; Morgan, Einon & Nicholas, 1975). However, when given a choice of exploring or not, they tend to emerge from a start-box slower than enriched animals (Morgan, 1973). Thus, various measures of exploration tend to be uncorrelated, indicating the problems of differentiating between exploration and mere locomotion. After having tried to organize the literature along such dimensions as "free" vs "forced" exploration, immediate and delayed (after differential rearing) testing and age at testing, I have arrived at the conclusion that these three classifications do not give a more systematic picture than the one presented in Table 1. However, one conclusion can possibly be drawn from Table 1. Several studies have converged towards the conclusion that post-weaning impoverishment causes a high rate of behavioral activity (Table 1B).

In a review of the effects of E and I rearing conditions on later learning (Gluck & Harlow, 1971), it was stated that no unequivocal conclusions concerning better learning after E or worse after I conditions could be drawn from the existing literature on non-primates. These authors (ibid.) proposed seven criteria that should be fulfilled for meaningful conclusions to be drawn, and found that virtually no study matched these criteria. Contemporary reviewers (Rosenzweig, 1971; Rosenzweig, Bennett & Diamond, 1972) also pointed at the inconsistency of the effects of post-weaning E conditions. Recently, however, there have appeared a number of better-controlled studies, yielding positive results for enrichment, so as to motivate Davenport (1976) to state

> "... a tentative conclusion that a fairly general learning capacity is increased by enrichment relative to impoverished rearing conditions" (p. 97).

Thus, the number of studies containing enrichment-facilitated learning is now well above three dozen. Also, the previously negative conclusions with regard to learning-facilitation in monkeys (Harlow, Harlow, Schiltz & Mohr, 1971) have now been questioned by Gluck, Harlow and Schiltz (1973).

In view of the availability of the mentioned recent reviews, only a selected part of the literature will be dealt with here. In Table 2, some studies absent from Davenports (1976) list are shown. The most widely used test of learning in the early rodent studies was the Hebb-Williams maze, and consistent results from this complex maze have been a facilitation of performance on the part of E rats (see Davenport, 1976, for a review). Whether this pattern reflects an improved "learning ability" (implying that emotional and motivational differences can be excluded) in E-rats is unclear. Firstly, many of the early findings of enhanced performance could have been a result of direct transfer of training from the E environment (Gluck & Harlow, 1971). Secondly, the error scores of the I groups may have been inflated by the previously documented tendency to an increased behavioral activity. A general opinion has been that only relatively complex tasks differentiate between enriched and impoverished animals (Rosenzweig, 1971). However, a spatial discrimination test yielded evidence of an E-induced facilitation (Nyman, 1967). Also, some recent studies (Doty, 1972; Freeman & Ray, 1972; Greenough, Yuwiler & Dollinger, 1973; Greenough, Wood & Madden, 1972; Ough, Beatty & Khalili, 1972) employing the Lashley III maze, active and passive avoidance and DRL 20-sec barpressing, have yielded evidence of beneficial effects of E rearing.

It has been found that postweaning I conditions result in a prolonged extinction of response-suppression among male rats (Caul, Freeman & Buchanan, 1974). If, as proposed by Morgan (1973; Morgan, Einon & Nicholas, 1975; Nielsen, 1970), social isolation and environmental impoverishment result in a reduced capacity for behavioral inhibition, i.e. these rats persist longer than controls in whatever they happen to be doing, this may account for some of the learning results reported (Caul, Freeman & Buchanan, 1974; Gardner, Boitano, Mancino, D'Amico & Gardner, 1975).

Conclusions. Enriched post-weaning rearing conditions give rise to a multitude of effects on cortical parameters. The increase of cell size and the number of glial cells as well as the effects on dendrite formation processes appear to be the most dramatic. Although a large amount of conflicting evidence exists, rearing in an impoverished condition seems to induce a high rate of behavioral activity and a deficiency of behavioral inhibition. Also, enriched rearing has been shown to result in a fairly general increase of learning test performance in several studies.

Table 2

Listing of Studies on the Effects of Differential Post-Weaning Experience on Learning in Normal Rats, Since Davenport (1976).

Reference	Treatment age(s)	Test + age(s)
Findings of enhanced learning test performance in enriched rats.		
Denenberg & Morton, 1962 b.	25-50	Hebb-Williams,60.
Schwartz, 1964.	0-95 (I), 5-95 (E)	Hebb-Williams maze, 135-137.
Ray & Höchhauser, 1969.	21-85	Lashley III maze, 95.Active avoidance, 100.
Brown, 1971.	25-105	Lashley jump stand, 105-123.
Tanabe, 1972.	25-60	Hebb-Williams maze, 100.
Wells, Geist & Zimmerman, 1972.	21-81	Hebb-Williams maze, 82 (?).
Caul, Freeman & Buchanan, 1974.	28-88	Conditioned lick suppression,115.
Gardner, Boitano, Mancino, D`Amico & Gardner, 1975.	21-82,21-93 (social and perceptual separated)	Passive avoidance, 87.
Will & Rosenzweig, 1976.	126-186	Hebb-Williams maze,187.
Will, Rosenzweig & Bennett, 1976.	25-65	Hebb-Williams maze,65-66.

4. ENVIRONMENTAL "THERAPY" FOR BRAIN AND BEHAVIOR DISTURBANCES

There is a considerable amount of experimental evidence indicating that the rearing environment affects many CNS and behavioral characteristics in animals (Section 3). In spite of this, only recently has there been a concentrated effort to "treat" brain and behavioral disturbances by means of "environmental therapy" (Walsh & Greenough, 1976).

Table 3 lists the available studies of this problem. A number of various insults, ranging from neocortical lesions over malnutrition to drug treatment has been used. The majority of studies indicate at least some degree of improvement after these insults in animals subjected to environmental enrichment both before and after weaning. Davenport (1976) has summarized the evidence concerning "environmental therapy" with disadvantaged rodent populations in the following manner: (1) All comparisons of learning scores between E and I conditions among the disadvantaged groups favor the E condition, (2) The E-I differences are larger among the disadvantaged animals than among the controls, (3) All studies and all measures of learning show a high degree of percentage of normalization, ranging between 33.3 and 115.9% (Davenport, 1976, p. 100). Thus, "environmental therapy" can be successfully applied to such disadvantaged populations and the disadvantaged populations profit more from environmental E conditions than do normal rats; "there is more room for improvement" (Davenport, 1976, p. 104) among the disadvantaged animals.

Among those studies added to Davenports (1976) listing in Table 3, there are apparently only two studies indicating small or non-existent effects of E-conditions (Bland & Cooper, 1970; Smith, 1959). However, Bland and Cooper (1970) delayed testing longer than in any of the other studies, which may have negatively influenced the results (Diamond, Rosenzweig, Bennett, Lindner & Lyon, 1972; Rosenzweig, 1971). Also, Smith (1959) did find an interaction of cortical lesion size and placement with rearing conditions, indicating that E rats, in direct opposition to I rats, were little affected by large posterior cortical lesions, but highly affected by small anterior lesions.

Utilizing super-enriched (S-E) (Kuenzle & Knüsel, 1974) post-weaning rearing conditions, Davenport (1976) and his collaborators have recently reported dramatic improvements of learning capacity in neonatally hypothyroid (cretinous) rats. Thus, maze acquisition and retention and bar-pressing extinction deficits in cretinous rats were almost totally

Table 3

Listing of Studies of the Effects of Environmental Enrichment on Behavior of Disadvantaged Rodents.

Reference and insult	Treatment age(s)	Test + age(s)
1 A. Studies of learning - positive findings.		
Schwartz, 1964.Day 0 bilateral posterior cortical lesions.	0-95 (I) 5-95 (E)	Hebb-Williams maze, 135-137. Lesion x Environment interact.
Hughes, 1965.Day 66 antero-dorsal postero-ventral hippocampal + dorsal cortical lesions.	33-66	Hebb-Williams maze, 80.
Ray & Hochhauser, 1969.Prenatal Days 3-19 growth hormone.	21-85	Lashley III maze,95. Hormone x Environment interaction.Conditioned avoidance,100.
Tanabe, 1972.Prenatal and preweaning low-calorie diet.	25-60	Hebb-Williams maze, 100.
Wells, Geist & Zimmerman, 1972.Day 0-77 low-protein diet.	21-81	Hebb-Williams maze, 82 (?).Diet x Environment interaction.
Schaefer, Buchanan & Ray, 1973. Day 0-18 para-chlorophenylalanine.	28-79	Conditioned avoidance, 83-84.
Coyle & Singer, 1975 a.Premating Day 14 - prenatal Day 21 imipramine.Prenatal Days 8-10 vitamin A.	25-60	Henderson maze,76. Swim maze,65-66,125-126.
Davenport, Gonzalez, Carey, Bishop & Hagquist, 1976. Prenatal Day 17 - Day 10 thiouracil.	36-70	Symmetrical maze, 80-132,200-210.
Will & Rosenzweig, 1976. Day 120 bilateral occipital cortical lesions.	126-186	Hebb-Williams maze, 187.
Will,Rosenzweig & Bennett, 1976. Day 0 occipital cortical + hippocampal lesions.	5-65,25-65	Hebb-Williams maze, 65-66.

Continued.

Table 3 continued

1 B. Studies of learning - negative findings.

Smith, 1959. Day 20-25 or 95-100 anterior-posterior cortical lesions.	18-90	Hebb-Williams maze 46,121.Lesion x Environment interact.
Bland & Cooper, 1969. Day 0 posterior cortical lesions.	3-330	Visual discrimination, 331.
Davenport, Gonzalez, Carey, Bishop & Hagquist, 1976. Prenatal Day 17 - Day 10 thiouracil.	36-70	Passive avoidance, 148-152.

2 A. Studies of behavioral activity - positive findings.

Levitsky & Barnes, 1972. Days 0-56 low-protein diet.	0-49	Open-field,126. Diet x Environment interaction.Emergence test,130 (?).Diet x Environment interact.
Blizard & Randt, 1974. Days 0-42 low-protein diet.	0-42 (mice)	Open-field,90-124. Diet x Environment interaction for one strain only.
Coyle & Singer, 1975 b.Premating Day 14 - prenatal Day 21 imipramine.	25-60	Home cage test of E animals, 25-27, 80-83.

2 B. Studies of behavioral activity - negative findings.

Ray & Hochhauser,1969.Prenatal Days 3-19 growth hormone.	21-85	Open-field,86-91.
Schaefer, Buchanan & Ray, 1973. Day 0-18 para-chlorophenylalanine.	28-79	Open-field,80.

reduced by S-E rearing, although testing was delayed 3-5 months after the completion of S-E rearing.

Two studies of particular interest are those by Coyle and Singer (1975a, b). In the first, they gave oral doses of imipramine to rat females before mating and during gestation or vitamin A between Days 8 and 10 of gestation. The offspring were reared in post-weaning E or I environments. When tested in a Henderson type maze (a complex test of food-finding) and on a task of spatial discrimination in a water-maze, imipramine- and vitamin A-induced deficiencies of learning were apparent among those rats reared in the E condition only. These results contrast with findings of an improvement of learning in the E condition after other insults. It should be noted that both learning tests were extremely difficult for the animals, which may have resulted in "floor effects" influencing the results. However, the authors (Coyle & Singer, 1975a) suggest that the reason for the obtained results may be that the drug-treated animals were less able to interact with their respective environments than were controls. This would result in no drug-control differences among the I animals, since they had very little to interact with, whereas the enriched drug-treated rats would profit less from their rearing conditions than controls. A second study (Coyle & Singer, 1975b), entailed observations of imipramine-treated animals in the E environment. At 25-27 and at 80-83 days of age, the imipramine-exposed subjects were behaviorally less responsive to their cage-mates and to their physical surroundings. Also, imipramine-exposed rats failed to show the characteristic depth increase of the visual cortex, normally resulting from environmental E conditions (Section 3.2). Further observations of prenatally imipramine-exposed rats (Coyle, 1975) have indicated a significant retardation of behavioral development during the pre-weaning period, further underlining the unresponsiveness of the imipramine-animals.

The behavioral "neo-T_3/T_4" and the "prenatal-imipramine" syndromes are in many respects each others opposite. The neo-T_3/T_4 rat is characterized by an earlier eye-opening and an advanced development of behaviors appearing during the pre-weaning period. Also, it shows an elevated behavioral activity as early as 6 days of age (Schapiro, 1966). Furthermore, the neo-T_3/T_4 rat responds at an earlier age and with more mature evoked response potentials to environmental stimulation (Sections 2.1.2 and 2.1.4). Thus, if the explanation by Coyle and Singer (1975a) of the learning findings in prenatally imipramine-exposed rats has any

validity, the results of raising neo-T_3/T_4 rats in E and I environments during the pre-weaning period would be opposite to those found with imipramine-treatment. Thus, we expect significant behavioral and learning differences to obtain between thyroxine-treated and control animals in the I condition, and no difference among the E animals. This is so, since the neo-T_3/T_4 animals are supposedly better able to interact with their rearing environment than controls during the pre-weaning period, and they can thus profit more from the E-condition. Whatever the behavioral disturbances induced by the neo-T_3/T_4-treatment (behavioral hyperactivity, learning deficit) it is expected to be less pronounced among the rats in the E condition than among those in the I condition.

In the present thesis, two problems concerned with the "therapeutic" effects of environmental enrichment after neo-T_3+T_4-treatment will be investigated: (1) Can enriched pre- and post-weaning conditions be shown to reduce behavioral hyperactivity and learning changes in neo-T_3+T_4 rats? (Section 5.4.4); and (2) If so, are pre- and post-weaning enriched conditions equally effective in this respect? (Section 5.4.5).

Conclusion. "Environmental therapy" for various disadvantaged rodent populations has been shown to result in marked improvements of learning among the disadvantaged-enriched groups. Reasoning from findings concerning the learning-effects of prenatal imipramine-treatment (Coyle & Singer, 1975a, b) some predictions are derived with respect to the influence of rearing conditions on behavior and learning of neo-T_3/T_4 animals.

5. EXPERIMENTAL STUDIES

The following section consist of three parts: (1) a short summary of Studies I-IV, (2) discussions of problems attacked in the present thesis, and (3) a theoretical framework.

5.1. Problems

In Section 2.2 effects of neo-T_3/T_4-treatment on adult animals were summarized. Some findings are empirically well supported: a lower weight of body and several major organs, secondary hypothyroidism and learning deficiencies. Also, some indications of a higher degree of behavioral activity in the open-field test have been reported. In this area, the following problems will be investigated: (1) Is the behavioral hyperactivity after neo-T_3+T_4-treatment a lasting and replicable phenomenon? (2) If so, what are some of its properties? (3) Does the learning deficiency hold across tests of differing complexity?

In Section 4, it became obvious that neonatally induced brain and behavioral disturbances can be counteracted by environmental enrichment during the pre- and post-weaning periods. In this particular area, the following problems will be attacked: (4) Can enrichment of rearing conditions be shown to reduce or eliminate the behavioral hyperactivity and learning changes in neo-T_3+T_4 rats? (5) If so, are pre- and post-weaning enriched conditions equally effective in this respect? (6) Can a plausible theoretical model of the behavioral and learning changes in neo-T_3+T_4 rats be supported from the data on neo-T_3+T_4 x rearing conditions interactions?

5.2. Experimental manipulations

In the studies reported below, newborn rat pups were randomly redistributed to the mothers within 24 hrs after birth, in order to balance genetic and prenatal differences between biological (born) litters. In Study IV, an additional procedure was added: as many biological litters as possible should be represented in the total group of pups, and each experimental litter should contain pups from all biological litters. On Day 3 (Studies I and IV) or Day 4 (Studies II and III), intraperitoneal injections consisting either of high doses of T_3 or T_4 alone (Study I) or of a mixture of T_3 and T_4 (T_3+T_4) were given either to half the number of pups in each litter (Study I) or to half the number of litters in each experiment (Studies II-IV). Control rats received saline vehicle.

The following rearing conditions were employed: In Study I, standard laboratory conditions, consisting of pre-weaning group cages and post-weaning group and individual cages were employed for all animals. In Studies II-IV, differential rearing was attempted for half of the animals. Thus, in all experiments, the E condition consisted of a wire-mesh cage, provided with numerous playthings, a ladder and an activity wheel. The I condition consisted either of identical (to E) barren cages (Study II: Exp. 1) or opaque plastic boxes with wire-mesh tops (Study II: Exp. 2 and Study III). These conditions were imposed during the pre-weaning period. In Studies II and III, no difference with respect to the number of animals existed between E and I conditions. The variables differentiating E and I conditions can be best described as being of a perceptuo-motor character, since visual exploration of the extra-cage environment was excluded and no objects were available in the I condition. The I environments in Exp. 1 (9-12 animals per cage) and Exp. 2 (8 animals per cage) of Study II differed somewhat with respect to space, resulting in a slightly better opportunity for motor exercise in Exp. 1. In Study IV, differential rearing took place during the post-weaning period. The E condition was identical to that used in Studies II-III, with the restriction that four animals were placed in each cage. The I condition consisted of standard individual cages with a reduced opportunity for visual exploration. Thus, the I-animals in Study IV (post-weaning) were also deprived of social interaction with peers. Two reasons for this difference between E and I conditions in Studies II/III and IV is that (1) social isolation is not feasible during the pre-weaning period, since this would result in a confounding of differential rearing with nutritional variables, and (2) in Study IV, the E-I difference in social interaction was included in an effort to parallel the conditions usually provided in post-weaning studies of differential rearing (cf. Section 3.2). Section 5.4.5 contains a further discussion of the importance of this E-I difference in Study IV as contrasted to Studies II/III.

Weaning took place on Days 23, 24, or 28 in the different experiments. Post-weaning differential rearing took place between Days 24 and 47.

5.3. Behavioral tests

In Studies I, II, and IV, an open-field (O-F) test was employed to assess differences of behavioral activity. Age at testing varied between 90 and 210 days. The O-F test was run for four consecutive days (Study

IV: six) four min each day, and ambulation, rearing, and defecation, and, in Study II: Exp. 2 grooming, were recorded. These variables were scored either on a per-day or on a per-minute basis.

Since the introduction of the O-F test (Hall, 1934) it has been widely used to assess both "emotionality" and "exploration" (see Archer, 1973; Walsh & Cummins,1976a, for reviews). It has become increasingly clear that neither of these constructs can be measured by single or multiple behavioral O-F indices. In the present thesis, the O-F test is used to measure the responses of rats to a novel environment, and the changes of these responses over repeated exposures to the environment, without reference to the constructs "emotionality" and "exploration". This approach is similar to that suggested by Archer (1973) for an "emotionality" use of the O-F test. The two behaviors chosen, ambulation and rearing, have been shown to decline reliably over successive exposures (Archer, 1973, pp. 229-230) and this decline is construed in terms of a behavioral habituation process. The main interest is to determine how the animals adopt to a novel test situation, since it may well be that the initial reactions and subsequent behavioral changes may contribute to the performance of animals in learning tests (cf. Bronstein & Spear, 1972; Smith, 1972).

Several learning tests were employed in Studies III and IV. Thus, a T-shaped water-maze was used to train a position discrimination (left-right) habit in Study III. After position discrimination training (original training: OT) three reversals of position were employed (R1, R2, and R3), requiring the animal to learn to swim to the position opposite to the one in the previous experimental phase. The number of trials, errors, and error-trials to a criterion of ten out of ten consecutive correct responses were recorded. Also, the mean final error trial for each successive criterion of 1-10 consecutive correct responses, and the number of perseverative responses made in the direction of the alternative correct during the previous phase before reaching Criterion 1 in each new reversal phase, were recorded.

In Study IV, a standard two-way active avoidance test, requiring the animals to jump from one side to the other of a box in order to avoid shock to the feet, was used. The number of avoidance responses, the number of jumps between trials (inter-trial crossings: ITC) and total and escape-latencies were recorded. A passive-avoidance test, requiring the animals to refrain from entering a dark compartment, after having received shock there 24 hrs earlier, was used. The number of animals

entering, and the time spent in the dark compartment were scored. Also, ambulation, rearing, and defecation in an adjacent open-field space were recorded on the training and test days. During the training phase of the Hebb-Williams maze, six problems of finding the way to food through a set of barriers were administered. Exit time - the time taken to enter the maze after the door of the start box had been opened, was scored. During the testing phase, food-finding problems number 1, 3, 9, 8, and 10 (Rabinovitch & Rosvold, 1951) were administered in that order, one problem each day. Running time - the time taken to reach the goal box after entering the maze, entries - the number of floor squares entered with all four feet, and errors - the number of error-lines crossed with the front legs were scored.

5.4. Discussion of problems

5.4.1. Is the behavioral hyperactivity after neo-T_3+T_4-treatment a lasting and replicable phenomenon? An answer to this question can be obtained from the results in Studies I, II, and IV. In Study I, significanly elevated ambulation and rearing rates were seen among males and females as late as 150 and 210 days after the neo-T_3+T_4-injection, in three separate experiments. The results for the males were more stable than for females, and were obtained with single high doses of T_3 as well as T_4. In Study II, essentially the same results were obtained in two experiments, and in Study IV, an elevated rate of both ambulation and rearing were seen at 63-69 as well as at 112-118 days. Defecation was in no case affected by the experimental treatment, nor was grooming behavior (Study II: Exp. 2).

In Study IV, several variables recorded in the learning tests can be used as indicators of the rate of behavioral activity. Thus, in the active-avoidance test, neo-T_3+T_4 rats (particularly females) performed significantly more inter-trial crossings. Also, shorter total and escape-latencies were obtained for the T groups. The former observation is indicative of a faster response to an external danger signal, and the escape-latencies may reflect an increased sensitivity to shock. In the passive-avoidance test, rearing scores were found elevated in the T groups on both days of testing. In the Hebb-Williams maze, faster running times on problems 1, 3, and 8, and more entries/min on all problems indicate the generally higher rate of behavioral activity in neo-T_3+T_4 rats. Thus, we conclude that behavioral hyperactivity is general across: groups of neo-T_3+T_4 rats, experiments, experimenters (three different

experimenters), varying degrees of E-I differences (Sections 5.2 and 5.4.5), and testing situations.

The above results agree well with the few reports on behavioral activity in neo-T_3/T_4 rats (Section 2.2.2). The fact that no effects were observed for defecation scores, may partly have been due to the low degree of visual, auditory (and thermal) stimulation present in the O-F situation. When the O-F test is used to measure "emotionality", high levels of noise and light are often presented (e.g. Archer, 1973). The finding of no-effect on defecation indicates that "emotionality" is not altered by neo-T_3+T_4-treatment (cf. Lát & Gollová-Hémon, 1969). This conclusion is of interest, since it may indicate that neo-T_3+T_4-treatment does not affect adult O-F behavior through the same mechanism as does non-specific neonatal stimulation ("handling") (e.g. Daly, 1973; Denenberg, 1964; Goldman, 1969).

How can the hyperactivity be accounted for? Besides Rastogi and Singhal's suggestions (1976a, b) that an enhanced synthesis and utilization of brain catecholamines may underlie this phenomenon, no other explanations have been proposed. Barnett, Smart and Widdowson (1971) mention three possibilities to explain hyperactivity in neonatally malnourished rats: (1) A lower threshold of arousal by all kinds of environmental stimulation, (2) An elevated responsiveness to novel stimuli in particular, and (3) A slower rate of habituation to environmental stimuli. These possibilities will be considered in Section 5.4.2 below.

5.4.2. What are the properties of the behavioral hyperactivity in neo-T_3+T_4 rats? In Study I (Exp. 1) the animals were first tested in the O-F situation at 150 days and later re-tested at 210 days. At the second testing, the female T rats were found not to differ from female C rats. If re-testing is considered as a way of reducing the novelty of the testing procedure, this finding raises the possibility that test-familiarization, at least in female T rats, reduces the O-F hyperactivity. This hypothesis is identical to proposal (2) by Barnett, Smart and Widdowson (1971) (see above). In Exp. 2 of Study I, this proposal was investigated by "handling" all animals for ten days prior to O-F testing. This resulted in no difference among female T and C groups, thus supporting the above hypothesis. A further test of this possibility was indirectly tried in Study IV, where Group I (replication I) was tested in the O-F prior to all other behavioral testing, and Group II (replication II) was tested in the O-F after extensive maze testing. In Group I, O-F ambulation and rearing were elevated for both sexes of neo-T_3+T_4 rats.

In Group II, neo-T_3+T_4 males evidenced higher ambulation and rearing whereas females showed an increase of ambulation only. Thus, although the support is not entirely consistent, prior "handling" and maze testing as well as re-testing reduced the hyperactivity among T females. This supports hypothesis (2) by Barnett, Smart and Widdowson (1971).

The third hypothesis proposed by these authors (ibid.) explains hyperactivity in terms of a slower habituation to environmental stimuli. The possibility that a slower habituation is shown by neo-T_3+T_4 rats over days of O-F testing was examined in Study II (Exp. 2). An interaction of Thyroxine x Rearing Conditions x Days appeared for ambulation among females, revealing that the CI and CE groups showed significant decreases over days, whereas the TE group showed an increase and the TI group did not change at all. In Study IV significant TE > CE differences were ap parent for Days 2-6 for ambulation (Groups I and II, males) and rearing (Group I, males). Also, rearing among Group I females showed the same pattern: no initial difference, but over-all differences depending upon a slower decrease of activity in neo-T_3+T_4 animals. For Group II males, the TE group alone did not change its rate of ambulation across days. An Index of Habituation (IH) was computed from the data in Studies II (Exp. 2) and IV. In Study II it was found that the TI group habituated their O-F activity slower across days than did the CI group. In Group I of Study IV, the same pattern was true for females, whereas there was a reversal (TI < CI) among the males. Thus, at least among the I rats (pre- or post-weaning), neo-T_3+T_4-treatment resulted in a slower habituation rate across days.

The discussion has so-far centered on activity changes across days. However, changes across minutes of testing were analyzed in Studies II (Exp. 2) and IV. In Exp. 2 of Study II, rearing rates were higher in male and female neo-T_3+T_4 rats for Minutes 2 - 4. In Study IV, there was a significant increase of rearing rate over minutes in the Group II T males, but no increase among the C males. Thus, across minutes of testing, the same pattern of no initial T-C difference, followed by a higher activity among the T rats, does appear.

In conclusion, from the available data, we can support the suggestions concerning an elevated responsiveness to novel stimuli (among females) and a slower rate of habituation to environmental stimuli as causes of the behavioral hyperactivity among neo-T_3+T_4 rats.

5.4.3. Do neo-T_3+T_4-induced learning deficiencies hold across tests of differing complexity? In Study I, it was proposed that the relative

difficulty of the learning test may interact with the neo-T_3/T_4-treatment in a specific manner. Thus, in complex tests, where neo-T_3/T_4 rats have been clearly shown to be deficient (Section 2.2.3), their hyperactivity could have compromized their performance (cf. Murphy & Nagy, 1976c). Performance on all tests of learning are presumably not equally "sensitive" to behavioral hyperactivity. Thus, scores on tests permitting a high degree of running behavior (e.g. the Hebb-Williams maze) may be more influenced than scores on a simple T-maze. Test-space may thus be a critical variable. However, there are a number of other test characteristics which may render tests more or less "sensitive" to behavioral hyperactivity. The most obvious is perhaps whether or not a high rate of behavioral activity is compatible or incompatible with efficient solution of the problem at hand. High random activity is e.g. not compatible with efficient learning in the Hebb-Williams maze, but highly compatible with rapid acquisition of a conditioned avoidance response. Tests also differ with respect to other variables such as: appetitive vs aversive motivation, active vs passive responding and the number of cues available for learning the task. Thus, it is almost inconceivable to produce a single "dimension" on which all tests of learning can be distinctly placed. However, for the present purpose, I propose a crude "dimension" of test "complexity" in terms of the number of trials required for attainment of a certain criterion of learning. If it takes 50 trials to reach the criterion 10 correct responses in a row on one test, and 25 to reach the same criterion on another, the first one is more "complex" than the second. Thus, the criteria for learning must be roughly comparable, for what reason not all tests can be easily compared. However, the one-way avoidance test would be considered less "complex" than the two-way avoidance test. For rats particularly, spatial discrimination tests would be considered less "complex" than visual discrimination tests. Defined in this manner, "complexity" becomes a relative property, only defineable in relation to another test. However, in order for predictions of how "sensitive" tests are to the influence of behavioral hyperactivity, a judgement has to be passed as to the compatibility/incompatibility of behavioral hyperactivity with efficient learning. This judgement has to qualify the asessment of "complexity". Even then, some tests may be little "sensitive" to behavioral hyperactivity in one version, and more so in another version. E.g. the passive-avoidance test, involving a test of an animal's ability to refrain from stepping off a platform after having received a shock on the floor below earlier, must

be considered very "sensitive" to hyperactivity, since it is essentially a test of the animal's ability to "sit still". In another version (Study IV), where the animal may run around in an adjacent open-field space instead of entering a compartment where it was previously shocked, performance may even be facilitated by high behavioral activity. Thus, predicting whether or not behavioral hyperactivity results in detrimental effects on learning or even a facilitation, becomes a complicated matter. However, we proceed with the two criteria given above: (1) the number of trials to criterion and (2) the compatibility/incompatibility of hyperactivity with learning test performance. The most relevant use for the proposed "dimension" is perhaps when different phases of a test are compared.

It was thus predicted that neo-T_3/T_4 rats may show a facilitation of performance on certain tests, and that no difference would be apparent on other, somewhat more "complex" tests. And, in agreement with Davenport and Gonzalez (1973), only relatively complex tests would evidence an inferior performance on the part of neo-T_3/T_4 rats. However, the reason for the latter statement on my part is not that the neo-T_3/T_4 rats are supposed to have a general trait of "deficient learning ability" which requires certain environmental circumstances to show up. Rather, this is only one example of the complex relationship between neo-T_3/T_4-treatment and learning test characteristics.

Studies III and IV are directed partly to this problem. In Study III, a test of spatial discrimination was used. The variable of "test complexity" was included within the learning situation. To that end, an initial position discrimination (OT) and three subsequent reversals (R1-R3) were employed. The initial position discrimination is rapidly acquired by rats, whereas the first reversal in particular, requires a larger number of trials. Also, the OT phase was made even easier by designating the initially preferred arm as the correct one for each rat (see Study III), Thus, it is expected that the direction and magnitude of the difference between neo-T_3+T_4 rats and controls will depend on the particular phase of the experiment (see Study III, p. 516).

The position discrimination and reversal task failed to show an overall deficient performance among the T rats. There were even signs of an improved performance (trials to criterion) on the part of the TI rats, although the difference is numerically small. In the OT phase, female T rats showed lower mean final error trial scores for Criteria 8-10 as compared to C females. During R1, however, the TE group showed higher scores

than the CE group for Criteria 9-10. Thus, during the more difficult R1 phase, the TE rats performed less well than the CE rats. In the R3 phase, the T group performed better than the C group for Criterion 10 only. The over-all pattern thus supports the conclusion that T rats show an enhanced performance in the OT phase, worse in the R1 phase and a progressively better performance during R2 and R3, However, the effects are small and inconsistent and depend upon sex as well as rearing condition and are therefore badly in need of replication before too much weight is given to them.

Analysis of initial perseverative errors after each reversal indicates that the TI > CI mean final error trial difference among females for Criterion 1 of the R1 phase is likely to result partly from initial perseveration by the TI rats. In the R2-R3 transition there was a TI < CI difference among males, indicating that the TI rats had less difficulty changing to the correct alternative than the CI group.

The error scores from Hebb-Williams testing in Study IV indicate that the T group performed significantly better than the C group on problems 1 and 3, but worse on problems 8, 9, and 10, thus seemingly supporting the above suggestion. It is of great interest that this Thyroxine x Problems interaction appears only if errors from all 4 runs/problem are included in the analysis. This may indicate the role played by initial exploration in producing the phenomenon.

The two-way active-avoidance test in Study IV did not show any effects of neo-T_3+T_4-treatment on the number of conditioned avoidance responses, although there was a slight numerical difference in favor of the T group (T: 5.7, C: 4.9). As pointed out before, there was a higher number of inter-trial crossings in the T group and, for the I group, faster escape- and total latencies among T rats. In the passive-avoidance test there were no T-C performance differences. This version of the test permits a high degree of behavioral hyperactivity in the adjacent open-field space as an alternative to entering the previously shocked compartment, for what reason the hyperactivity in the T group should have been expected to facilitate its performance (cf. Study IV, p. 9, for a detailed description of the test). These results for passive avoidance are in contradiction to findings by other authors (Davenport & Gonzalez, 1973; Stone & Greenough, 1975), but they used versions of the test, which were definitely tests of the ability to "sit still".

In conclusion, the water-maze data give only weak support to the hypothesis of a neo-T_3/T_4 x test "complexity" interaction, within the test.

However, the over-all trials to criterion performance supports it. The Hebb-Williams maze data contain supporting results. Comparisons of learning differences between tests: passive-avoidance vs spatial discrimination vs active avoidance vs Hebb-Williams maze in the present studies, tend to support the hypothesis, although a performance facilitation was expected in the passive-avoidance test. A comparison between tests used by other workers (Study I, p. 55) also supports the hypothesis. However, the proposed "dimension" of "complexity" may be too crude to catch more subtle differences between tests and needs refinement.

The initial impetus for the neo-T_3/T_4 x test "complexity" interaction was the observation of a behavioral hyperactivity in the T group. No attempts have been made in the present studies to investigate the possibility of a correlation between activity socres and learning scores on certain tests, due to the heterogenous pattern of findings on the learning tests. Still, the Thyroxine x Problems interaction for Hebb-Williams errors (Study IV) was evident only when data from all 4 runs/problem were included, which may point to the importance of initial exploratory activity for this phenomenon.

5.4.4. Can enriched rearing conditions be shown to reduce the behavioral hyperactivity and learning changes in neo-T_3+T_4 rats? In Section 4 it was shown that enriched rearing conditions have been used to reduce learning deficiencies induced by neonatal insults. Studies II-IV are designed primarily to investiate the possibility that pre-weaning (Studies II and III) and/or post-weaning (Study IV) E conditions can reduce neo-T_3+T_4-induced behavioral hyperactivity and learning changes. The initial impetus for these studies was a theoretical model for the explanation of neo-T_4-induced learning deficits in adult rats, proposed by Schapiro (1968, pp. 225-226; 1971b, p. 67; Schapiro, Salas & Vukovich, 1970, p. 149). Schapiro pointed out that neo-T_3/T_4-treatment results in an acceleration of the behavioral development in the rat (Section 2.1.4) and that the pre-weaning developmental periods of many behaviors are compressed in time (cf. also Sections 2.1.1 and 2.1.2). He further hypothesized that there was a concomitant compression of the ontogenetic periods characterized by a high degree of neural and behavioral plasticity and a gradual acquisition of an expanding behavioral repertoire. In a sense, the neo-T_3/T_4 animals would have a shorter time-period during which they would be optimally sensitive to environmental stimulation. This compression of important periods of infancy in the rat was suggested by Schapiro to underlie the adult learning deficiencies of neo-T_3/T_4 rats.

He (Schapiro, 1971a) specifically pointed to the pre-weaning period as being the most sensitive period for affecting CNS modification by environmental-experiential means.

In Studies II-IV, four groups of rats were included: TI, CI, TE, and CE, thus designated according to their hormonal treatment and rearing condition. The method of investigating the question of E-compensation of neonatally thyroid-hormone-induced behavioral disturbances in Studies II-IV has been to subject the data to analysis of variance, in order to analyse Thyroxine x Rearing Conditions (T x RC) interactions. The pattern: TI > CI, TE = CE, underlying T x RC interaction has been considered as a support for Schapiro's model. Thus, if E-rearing reduced the neo-T_3+T_4-induced disturbance, the model was considered supported. However, T x RC interactions can obviously result from (1) other relationships between TI, CI, TE, and CE groups, e.g. TI > CI, TE < CE; TI = CI, TE > CE, and (2) several different changes of relationships between the groups can result in the TI > CI, TE = CE pattern, e.g. if group CE has a very high score or if CI > CE. Alternative (1) will be discussed in Section 5.4.6. Alternative (2) for behavioral hyperactivity may result from the CI group showing a lower rate of activity than all other groups, or from the TI group showing a much higher rate. An argument for an E-induced lowering of the behavioral activity in the T group requires a decrease in the TE group with the CI and CE groups remaining on a fairly equal level or CI > CE. In order to deal with these complexities, a numerical index, expressing the degree of E-effect in the T groups in relation to the thyroid hormone-effect in the I condition for a particular dependent variable has been developed (cf. Davenport, 1976): TI-TE/TI-CI. This index has not been used in Studies II-IV, but will be employed in the present discussion. Table 4 contains numerical values for the above index for a selection of dependent variables from Studies II-IV, where, in most cases chosen, significant T x RC interactions have been obtained. In Table 4, the index-values are multiplied by 100 to give "percentage normalization". This figure will approach 100 when the E-effect in the T groups approaches the magnitude of the T-effect in the impoverished groups. Thus, it may exceed 100. It should be noted that the percentage normalization figure is independent of the value for the CE group.

With Schapiro's model in mind, Study II was designed to investigate whether or not the provision of a higher degree than normal (in the laboratory) of environmental pre-weaning stimulation would reduce the be-

Table 4

Percentage Normalization : TI-TE/TI-CI x 100 for Several Behavioral Variables.

		Males	Females
Study II			
Open field[a]			
Exp. 1	Ambulation	7	94
	Rearing	47	113
Exp. 2	Ambulation	65	33
	Rearing	88	0
Study III			
Water-maze.Mean final error trial[b]			
OT	C 10	350	22
R1	C 1	58	138
R1	C 10	-686	280
R2	C 1	2	200
R2	C 10	78	205
R3	C 1	100	157
R3	C 10	45	75
Water-maze.Perseverative responses[c]			
OT-R1		50	162
R1-R2		250	55
R2-R3		52	367
Study IV[d]			
Open field			
Group	Ambulation	-575	7
I	Rearing	-1100	27
II	Ambulation	19	16
	Rearing	25	9
I	IH	65	-11
II	IH	-1867	74
Hebb-Williams			
II	Running-time	2	8
II	Entries/min	25	2
II	Errors	53	-135
Active avoidance			
I	Total latency	33	18
I	Escape latency	100	18

a) Cf.Table 1, Study II; b) Cf.Table 1, Study III; c) Cf. Table 2, Study III; d) Cf.Table 2, Study IV.

havioral hyperactivity in neo-T_3+T_4 rats. Although Schapiro explicitly discussed only the learning deficiencies in neo-T_3/T_4 rats, in Study II, it was suggested that behavioral hyperactivity should also be incorporated into the model. In Exp. 1, there were T x RC interactions among the females for ambulation and rearing. These were due to a TI > CI, TE = CE pattern for ambulation, and a TI > CI, TE < CE pattern for rearing, (The latter pattern can be considered as a "stronger" version of the first, and is thus also accepted as a support for the model.) Table 4 shows that percentage normalization was high in both cases. These findings indicate that the behavioral hyperactivity among female neo-T_3+T_4 rats may be specific to the I (or even to the standard laboratory rearing) condition, in that it is reduced or even reversed by enrichment.

In Exp. 2, there was a T x RC x Days interaction in the data computed per day of testing for ambulation in females. An inspection of Fig. 2 of Exp. 2 (Study II) reveals a larger difference between the TI and CI groups than between the TE and CE groups, indicating that E-rearing reduced the behavioral hyperactivity in the T group. However, percentage normalization is high only on Day 1 of testing (73%), and rather low on subsequent days (Days 2-4: 29, 31, and 18%, respectively), since the CI group habituated rapidly across days. An inspection of Table 2 of Study II (Exp. 2) shows that the TI-CI differences are in all cases approximately twice as large as the TE-CE differences, although significant T x RC interactions were not observed. Table 4-data reveals that normalization was high only among the males, and almost non-existent among females, which is in direct contradiction to the pattern in Exp. 1 of Study II. For the Index of Habituation, there was a T x RC interaction due to the fact that E-rearing seemed to completely eliminate the slowing of behavioral habituation evidenced by the TI group. However, an inspection of Fig. 4 of Study II shows that there was a larger E-effect in the control group than in the neo-T_3+T_4 group. Also, normalization was only moderately high: 47%. In conclusion, the previous section shows (1) that T x RC interactions in the form of TI > CI, TE = CE differences alone cannot give unequivocal evidence of "normalization"; (2) That pre-weaning enrichment can reduce behavioral hyperactivity in neo-T_3+T_4 rats, although the failure to replicate the data from Exp. 1, detracts from the generality of this conclusion; (3) A moderate amount of "normalization" was shown for behavioral habituation.

A further test of the Schapiro hypothesis concerning hyperactivity was performed in Study IV, where enrichment took place during the post-

weaning period. A T x RC x Days interaction appeared for ambulation in Group I males, due to a TE > CE (Days 2-6), TI = CI (Days 3 - 5) pattern. In Table 4, it is evident that percentage "normalization" was high, or rather, that there was an E-effect in the T group, but in a direction opposite to that in previous experiments. Close to identical T x RC x Days interactions appeared for rearing (Group I males) and for ambulation (Group II males). Percentage "normalization" was high only for rearing for Group I males, due to the absence of a TI-CI difference. Thus, post-weaning E-conditions were not only less effective than pre-weaning E-conditions (Study II), but rather "anti-therapeutic" in that the T-C differences were higher in the E condition than in the I condition in some cases (see Section 5.4.6 for a further discussion). In the Habituation-Index data, a T x RC x Sex interaction duplicated the TI > CI, TE = CE pattern from Study II among Group I females, but a TI < CI, TE = CE difference was seen among males. Percentage normalization was 65 for males and only 11 for females. This is further illustrated in Table 2 of Study IV, where it is evident that the E-I difference is much higher in the male T group than in the female T group. This, in combination with a large TI-CI difference in the female group results in the very low percentage normalization. The TI < CI, TE = CE pattern among males for Habituation Index indicates that post-weaning impoverishment can speed up the slow rate of habituation seen in neo-T_3+T_4 male rats. In spite of the absence of effects on Group II IH-scores, there were large "normalization" values in this group (Table 4). This illustrates that the TI-TE/TI-CI index must be preceded by statistical testing of interactions.

In the training phase of the Hebb-Williams test (Study IV), a T x RC interaction was seen for exit time, due to a TE < CE difference only, since the CE group showed a surprisingly high score. Percentage normalization was moderate: 41%. In the active-avoidance test, the total response latency revealed a significant T x RC interaction due to a TI < CI (Sessions 5-9), TE = CE (Sessions 1-5, 7-9) pattern. The interaction was mainly dependent on a high value of the CI group. The percentage normalization was 22 only. For escape-latencies, a T x RC interaction was due to a TI < CI, TE > CE pattern. Percentage normalization was moderate: 39%. Summing up, a moderate degree of post-weaning normalization was obtained for some activity variables, although widely different tests and variables were used to assess behavioral activity in Study IV.

Study III was designed in part as a test of T x RC interactions for

adult learning. Thus, pre-weaning enrichment was supposed to counteract whatever the neo-T_3+T_4-induced learning changes. A T x RC interaction was found for the over-all trials to criterion variable, due to a TI < CI difference and no TE-CE difference. Percentage normalization was 68. The direction of this difference is opposite to that implied by Schapiro (1968), since neo-T_3+T_4-treatment resulted in an improved performance. This does not detract from the conclusion that pre-weaning enrichment can counteract performance changes induced by neonatal hyperthyroidism. The argument only presupposes that whatever the mechanism for the performance-change, this mechanism is differentially affected by pre-weaning E and I conditions (see further discussion in Section 5.4.6). In the R1 phase, a T x RC x Criteria interaction for mean final error trials was due to a TE > CE difference for Criteria 9 - 10, and no TI-CI difference. A rather high value in the TE group resulted in a percentage "normalization" of 1200! This interaction is in the opposite direction to those previously seen, since the E-condition increased rather than decreased the T-C difference (see Section 5.4.6 for further discussion). In the analysis of initial perseverative responses, there was a T x RC interaction in the OT-R1 transition, due to a significant TI > CI difference and no TE-CE difference (an indication of a reversal: TE < CE is evident among females in Table 2, Study III). Percentage normalization was 103. In the R2-R3 transition, there was a T x RC x Sex interaction, due to a TI < CI difference among males only. Percentage normalization was 50. In Table 4, percentage normalization for the mean final error trial data in Table 1 of Study III and for initial perseverative responses in Table 2 of Study III are presented. It can be seen that mean final error trial normalization data vary widely, partly due to the reversal of the directions of the pattern of differences underlying T x RC interactions, and partly due to small TI-CI differences. Percentage normalization for perseverative responses is more stable, in that no values are below 50%.

In Study IV, Hebb-Williams maze testing errors revealed a T x RC interaction due to a TI < CI, TE > CE pattern. Thus, again, we see a neo-T_3+T_4-induced performance-deficit evident only among the enriched animals (see Section 5.4.6). Percentage normalization is shown in Table 4.

The conclusions below are based on T x RC interactions fulfilling the following criteria: (1) A significant T x RC interaction; (2) A normalization score above 45%; (3) The percentage normalization score must not be inflated by a minimal or non-existent TI-CI difference. Only T x RC interactions fulfilling these criteria will be considered in the follow-

ing sections.

In conclusion, pre- and post-weaning enriched rearing conditions in Studies II/III and Study IV, respectively, have given partly different results. It should be pointed out that the pre-weaning E-I difference was of a purely perceptuo-motor character, and that the post-weaning E-I difference consisted of perceptuo-motor as well as social enrichment-isolation. Discussion of this discrepancy is deferred to Section 5.4.5. For behavioral hyperactivity induced by neo-T_3+T_4-treatment, the following results were obtained: pre-weaning E-conditions reduced it and speeded up behavioral habituation in the open-field test, and post-weaning E-conditions induced behavioral hyperactivity in neo-T_3+T_4 rats. Also, post-weaning impoverished rearing conditions seemed to speed up the slow rate of behavioral habituation among males. These contrasting results will be discussed further in Section 5.4.6. For learning, neo-T_3+T_4-induced performance improvements in simple learning tests can be counteracted by pre-weaning enrichment. Also, perseverative responding in complex test phases seem to be normalized. In contrast, performance in more complex tests and test phases on the part of neo-T_3+T_4 rats is more deficient after pre- and post-weaning enrichment than after impoverished rearing conditions.

5.4.5. Are pre- and post-weaning enriched rearing conditions equally effective in alleviating the hyperactivity and learning changes? Although no statistical testing is possible, a comparison of effects in Studies II and III with the effects in Study IV yields some indications on this point.

As was pointed out in the conclusion of the previous section (5.4.4), pre- and post-weaning enriched rearing conditions have evidenced opposite results with respect to behavioral hyperactivity in neo-T_3+T_4 rats. Also, the results from learning tests indicate that pre- and post-weaning enrichment may partially affect different mechanisms of learning, although this conclusion is so-far a mere speculation since the learning-data on post-weaning enrichment are so few in the present studies that firm conclusions are hard to draw.

The fact that pre-weaning E-conditions were more efficient in reducing neo-T_3+T_4-induced hyperactivity than were post-weaning E-conditions may have several reasons. (1) Pre- and post-weaning differential rearing consisted of perceptuo-motor E-I differences. In addition, post-weaning differential rearing entailed a restriction of social interaction, in that the I animals were housed individually, whereas the E

animals were four/cage. However, the E condition was identical in all experiments, with the exception of the number of animals, which was 9-12 in the pre-weaning and 4 in the post-weaning conditions. (This difference was necessary in order to compensate for the growth of the animals, thus approximately equating the space available for each rat.) The assessment of enrichment-effects in the T groups is, however, not based only on the results from the (identical) E conditions. Rather, the following comparisons are involved (a) in the analysis of variance, first, all groups are compared to each other, when T x RC interactions are tested for statistical significance. Then, TI-CI and TE-CE differences are tested. Thus, in the latter, crucial testing, a comparison is performed only within environments. Thús, one way for I-I differences between Studies II/III and IV to influence TI-CI differences, would be by allowing a greater or smaller degree of expression of T-C effects. There is no a priori reason to expect this, and, in fact, an informal comparison shows, that the T-C effects are negatively correlated with the degree of impoverishment (see below). The second comparison involved (b), the percentage normalization, entails a TI-TE comparison which is thus performed between environments, and is later compared to a TI-CI difference. In this case, a certain degree of E-I difference during the pre-weaning period and another during the post-weaning could conceivably confound the conclusions concerning pre- vs post-weaning effects. For that reason, the TI-TE/TI-CI index is used only when significant interactions have been found. Thus, I consider it most unlikely that the I-I difference between pre- and post-weaning conditions confounds the conclusions with regard to the effectiveness of pre- and post-weaning enrichment in alleviating neo-T_3+T_4-induced behavioral hyperactivity. In fact, it could be argued that the inclusion of these I-I differences negatively biases the tests for pre- vs post-weaning effects.

To show this, the following line of reasoning can be pursued. The I environments can be ordered on a dimension of an increasing degree of impoverishment in the following order: first, Exp. 1, Study II (restriction of perceptual, and to some degree motor stimulation, since no objects were available in the I cages), second, Exp. 2, Study II and Study III (I condition consisted of a smaller cage), third, Study IV (a still smaller cage for the now larger post-weaning rat, and no cage-mates). The central problem is whether the social isolation and lesser cage space/animal imposed during the post-weaning period, is quantitatively or qualitatively different from the perceptuo-motor impoverishment during

the pre-weaning period. When designing Studies II-IV, the former position was taken, since social and perceptual impoverishment/enrichment have often been reported to yield similar effects on behavioral variables (Gardner, Boitano, Mancino, D'Amico & Gardner, 1975; Morgan, 1973). Also, it was assumed that, for differential rearing to be effective, the post-weaning rat needed a higher degree of E-I differences than the pre-weaning rat. The latter assumption was based partly on the stress laid by Schapiro and others (Bekoff & Fox, 1972; Schapiro, 1971a) on the pre-weaning period being more sensitive for the experiential/environmental modification of brain and behavior, and partly on experimental evidence showing larger effects of pre-weaning (than of post-weaning) differential rearing on brain characteristics (Altman,1970; Malkasian & Diamond, 1971; Schapiro & Vukovich, 1970). Thus, a greater degree of impoverishment was provided during the post-weaning period, since the CNS of post-weaning rats is less sensitive to environmental stimulation. In spite of the fact that a greater E-I difference was provided during the post-weaning period, a lesser degree (and partly different: see Section 5.4.6) of enrichment-induced modification of neo-T_3+T_4-effects was seen, when compared to the pre-weaning E-I difference, which resulted in greater enrichment-effects. Thus, the strength of the effects varies inversely with the degree of E-I difference.

The second reason for differential effects of pre- and post-weaning environmental manipulations is: (2) As was pointed out above, the E conditions were identical during both periods in the present studies. This particular degree of environmental enrichment may have been sufficient for the pre-weaning rat, but insufficient for the post-weaning animals. The findings by Davenport (1976) of a substantial reduction of behavioral hyperactivity in neo-T_4 rats by post-weaning "super"-enrichment (Kuenzle & Knüsel, 1974) support this contention. Thus, more complex and varied E-conditions in Study IV may have given rise to different effects. (3) Studies of neo-T_3/T_4 rats (Section 2.1.1) indicate a reduction of the number of nerve cells, advanced elaboration of neural processes, a decrease in the rate of dendritic spine formation and a retarded development of evoked cortical responses towards the end of the pre-weaning, and, most likely, during the post-weaning periods. Due to these disturbances, the neo-T_3+T_4 rats may respond less well or in a different manner to post-weaning as opposed to pre-weaning enrichment. This possibility is further considered in Section 5.4.6.

In general, the rather long delays imposed between differential

rearing and behavioral testing in the present studies, purposely employed in order to avoid direct carry-over effects from the respective environments (cf. Gluck & Harlow, 1971) and "emergence trauma" (Morrison & McKinney, 1976) may have reduced the possibilities of obtaining significant effects of environmental manipulations in general.

5.4.6. A model for the behavioral and learning changes in neo-T_3+T_4 rats. How can the activity and learning changes in neo-T_3+T_4 rats be accounted for? With regard to hyperactivity, this question was commented in Sections 5.4.1 and 5.4.2, and will be discussed again later in the present section.

In Section 5.4.4, the model proposed by Schapiro (1968) for neo-T_3/T_4-induced learning deficiencies was introduced. Also, it was suggested that the model should incorporate behavioral activity as well as learning. In Section 5.4.4 it was further suggested that performance improvements on learning tests should also be subsumed by the model. This is not entirely implausible for the following reason. Isaacson, alluding to parallel observations among humans (1976, pp. 363-364) has argued that the most "mentally retarded" animals are those who solve simple laboratory problems the fastest. An extensive literature documents that CNS - damage, e.g. to the limbic system lead to an improved performance on the two-way active avoidance test (e.g. Isaacson, 1974). Since neo-T_3+T_4-induced improvements of performance have been observed only on simple tests, it could be argued that this may be an effect of certain CNS-deficiencies. Besides these extensions, I have implicitly argued that (1) the model proposed by Schapiro is applicable to neo-T_3+T_4 rats as well as to neo-T_3/T_4 rats, (2) that the provision of enriched and impoverished rearing conditions to neo-T_3+T_4 rats constitutes a fair test of the model. How can the latter two proposals be supported? (1) One way of assessing the comparability of the neo-T_3+T_4 and the neo-T_3/T_4-preparations is to compare them with respect to different variables. The two kinds of rats have the following characteristics in common: a lower body weight (Studies I, II, IV), an earlier eye-opening (Study IV), a higher rate of behavioral activity (Studies I, II, IV), deficiencies of learning in some tests (Studies III, IV). In an unpublished study, we have also observed lower brain and testes weights (cf. Section 2.1) in neo-T_3+T_4 animals. Two characteristics may differentiate the two kinds of animals: improvements on learning tests have not been reported in neo-T_3/T_4-animals, and a deficiency of thyroid function has not been found in the neo-T_3+T_4 animals (cf.

Study I). Against this background, I argue that the neoT_3+T_4- and the neo-T_3/T_4-animals are sufficiently similar to allow the application of Schapiro's model to both. (2) The provision of enriched rearing conditions can be expected to counteract behavioral hyperactivity and learning deficiencies in view of the data summarized in Sections 3.1 and 3.2, showing that enriched post-weaning rearing often reduces hyperactivity (but see Table 1A for contradictory results) and improves learning (Table 2, and Davenport, 1976). Also, since active interaction with the enriched rearing condition and not mere passive exposure to it are essential, at least for brain changes (Ferchmin, Bennett & Rosenzweig, 1975), and an active interaction can be brought about by the provision of a varied assortment of objects and several cage-mates (Rosenzweig, 1971), differential rearing of neo-T_3+T_4 rats can be considered as a fair test of the Schapiro hypothesis.

The Schapiro model stresses the "negative" side of neonatal hyperthyroidism in particular. By this I mean that it is based on findings and arguments concerning a compression of important developmental periods in the rat, presumably resulting in a limitation of the later behavioral flexibility of the animals (Schapiro, 1971a). However, during the preweaning period, there is also a "positive" side of neonatal hyperthyroidism. Although it was repeatedly stressed by Schapiro (1968; Schapiro & Norman, 1967) that "neonatal thyroxine administration appears to advance the learning ability of the young rat" (Schapiro, 1968, p. 225), he apparently did not incorporate it into his model. The empirical support for this contention is better to-day than in 1968 (Murphy & Nagy, 1976b, for retention ability in mice; Stone & Greenough, 1975, reporting supporting as well as contradictory results). Several other findings also attest to the high neural and behavioral "competence" of the neonatally hyperthyroid rat during the early pre-weaning period. Thus, an earlier eye-opening, earlier mature EEG responses to external stimuli, earlier cortical evoked potential responses in the auditory as well as the visual systems, a higher rate of behavioral activity and an earlier maturation of cholinergic inhibitory functioning (in mice) have been reported (Sections 2.1.2 and 2.1.4). One may wonder why the neonatally hyperthyroid rat cannot interact more efficiently and at an earlier age with its rearing environment due to these advanced functions, thus compensating for the compression of later developmental periods. Obviously, the Schapiro model presupposes that this does not occur, at least not under normal (i.e. impoverished) laboratory rearing conditions. It is at the

core of the present argument that such a compensation does occur when enriched rearing conditions are provided. That it might not occur in the impoverished environment can be due to the fact there are very few things to interact with under such conditions.

So-far, the discussion has focused only on the pre-weaning period. What about the neural and behavioral "competence" of the neonatally hyperthyroid rat during the post-weaning period? From the argument of a premature termination of important ontogenetic periods for the experiential modification of brain and behavior, it follows that the post-weaning period should be characterized by a lower "competence" on the part of the neonatally hyperthyroid rat. In Sections 2.1 and 2.2, evidence in favor of this proposition was summaritzed. Thus, a significant decrease in the rate of cortical and cerebellar dendritic spine formation, a retardation of the development of cortical evoked responses, an impairment of retention capacity (in mice) and a lower number of nerve cells have been found. Also, the post-weaning T rat may be hypothyroid (Section 2.2.1) and learn less well than normal rats (Section 2.2.3) although the influence of the first of these factors on the interaction with the environment is unknown, and the age at which the second factor emerges remains to be determined (no post-weaning reports earlier than Day 35 are available). From the evidence cited above, it can be argued that the neonatally hyperthyroid rat can be expected to be less "competent" than normals during the post-weaning period. I propose that this lesser "competence" makes the post-weaning neo-T_3+T_4 rat less able to interact efficiently with its rearing environment.

To recapitulate, the neo-T_3+T_4 rat is able to interact actively with its rearing environment earlier than the normal rat and in a more active fashion during the major part of the pre-weaning period. Although the period of active interaction before weaning can be no more than 13-14 days, significant changes are expected to take place, provided that a richly stimulating environment is at hand. The higher "competence" gives few effects if the rats are reared in an impoverished environment, since there are very few sources of stimulation, besides cage-mates. In an enriched environment, however, the higher competence of the neo-T_3+T_4 rat gives as a result that the hyperactivity and learning deficiencies induced by neonatal hyperthyroidism may be compensated for. Although the major evidence of an enrichment-induced lowering of the behavioral activity level and a reduction of learning deficits pertain to the post-weaning period (Sections 3.2 and 4), it is considered likely that such

changes can take place also as a result of processes during the pre-weaning period (cf. Section 3.1). What predictions follow from this line of reasoning with respect to the Thyroxine x Rearing Conditions (T x RC) interactions? It is expected that the T and C rats in the I condition will differ with respect ot hyperactivity and learning as adults. Thus, the TI group will be more active than the CI group. In the E condition, the T group will not differ from the C group, provided that the C group does not profit equally from the E conditions as does the T group. That the latter is not likely can be argued partly from the higher "competence" of the T group. Thus, a TI > CI, TE = CE pattern can be expected to underlie T x RC interactions with respect to behavioral activity. Also, if the TE group profits more than the CE group, a TI > CI, TE < CE pattern can also be obtained. These two patterns will henceforth be referred to as the "A" pattern (TI > CI and TE = CE or TE < CE). (For speed and latency measures of behavioral activity in Study IV the < > -signs are reversed.) For learning, the problems are more complicated, since we have seen that T groups show an improved performance on certain tests (Section 2.1.4 and Studies III-IV). By rashly subsuming performance deficits on complex tests tests and performance improvements on simple tests (cf. Isaacson, 1974), the following line of reasoning can be pursued. Let the expression TI > CI denote that the TI group performs more errors on complex tests or fewer errors on simple tests. Then, we end up predicting the same pattern of TI > CI, TE = CE or TE < CE differences as for behavioral activity.

Having defined one pattern of differences ("A") underlying T x RC interactions we may proceed to considering the post-weaning period. As has been pointed out previously, the end of the pre-weaning period and the first part of the post-weaning period are most likely characterized by an "incompetence" on the part of the neo-T_3/T_4 rats. If these rats interact less efficiently with their post-weaning environment, what can be predicted about the pattern of differences underlying T x RC interactions? In the studies by Coyle and Singer (1976a, b) the drug-(D)treated rats were shown to interact less well with their rearing environment, and were also shown (Coyle, 1975), to have a slower rate of behavioral development. The pattern of differences found by Coyle and Singer (1976a) was DI = CI, DE > (indicating a deficient performance on learning tests) CE. The reason for this pattern (particularly the DI = CI part) is that learning deficiencies caused by the drug used (imipramine) generally do not show up under normal laboratory conditions (Coyle & Singer, 1976a). With neo-T_3+T_4 rats this is, however, not the case, since reliable T-C

differences do develop under normal laboratory conditions (Sections 2.2.2 and 2.2.3). Thus, the pattern to be expected if the post-weaning neo-T_3+T_4 rats are less "competent" than normals is rather TI > CI (because the groups in the I condition have had very little to interact with), TE > CE (since the T group cannot profit from the E conditions properly). Consequently, we should see no T x RC interactions if this was the case. As is evident from Study IV, interactions appear also after post-weaning differential rearing (see below). However, our interest at this point should not be to investigate interactions but to look for main effects of neonatal thyroid-hormone treatment. In the data from Study IV, there are a number of main effects of neo-T_3+T_4-treatment which are not qualified by higher-order interactions. Furthermore, these main affects are in the direction of a higher rate of behavioral open-field activity, faster running times, and more entries/min on Hebb-Williams problems, more intertrial-crossings in the active-avoidance test, a higher rearing rate in the open-field space of the passive-avoidance test, all indicating the higher rate of behavioral activity in neo-T_3+T_4 rats. Also, main effects of neo-T_3+T_4-treatment showing fewer errors on relatively easy Hebb-Williams problems (1 and 3) and more errors on relatively difficult problems (8, 9, and 10) were observed. Thus, provided that other reasons for the relative lack of effects of post-weaning environmental enrichment on neo-T_3+T_4-induced behavioral and learning phenomena can be ruled out (see Section 5.4.5 for these "other reasons"), the hypothesis of a lower degree of "competence" on the part of post-weaning neo-T_3+T_4 rats can be supported from the Study IV-findings.

The pattern of differences underlying T x RC interactions referred to above as the "A" pattern covers all interactions obtained in the pre-weaning enrichment studies (Studies II and III) for open-field ambulation, rearing and habituation, for fewer perseverative errors and fewer trials to criterion in the simple phases of the water-maze and for more errors in the complex phases. That these particular variables are covered by the "A" pattern is self-evident, since it was defined to do so. However, it is notable that it is a strictly pre-weaning pattern. Using pattern "A" as a basis, we can support the Schapiro model with regard to the pre-weaning period. The extensions proposed in the present discussion give a broader base for the model and extend it to other behavioral phenomena and hormonal treatments than those originally used by Schapiro.

Besides the main effects pattern (TI > CI, TE > CE in Study IV, there is a pattern of differences underlying interactions, provisionally

called "X": TE > (denoting a higher behavioral activity, and more errors on complex tests of learning)CE, TI = CI or TI < CI. This patterns holds for T x RC interactions for open-field ambulation and rearing (Study IV), learning in the R1 phase of the water-maze test, and for learning in the Hebb-Williams maze. An account of the reasons for this pattern cannot be readily obtained. After having tried out several different explanations of behavioral changes in neo-T_3/T_4- animals, e.g. secondary hypothyroidism (Eayrs, 1968), the lower number of postnatally formed nerve cells (Balázs, Kovács, Cocks, Johnson & Eayrs, 1971) and a foreshortening of the ontogenetic period during which fine-grain tuning of the brain takes place (Stone & Greenough, 1975), I have found none of them compatible with the above pattern of differences. There remains the speculative possibility that the phenomena covered by pattern "X" are different from those seen after neo-T_3/T_4-stimulation in the normal laboratory environment, thus being more like the imipramine-induced deficits reported by Coyle and Singer (1976a). However, only further replication of these findings can shed light on the problem.

5.5. Conclusions

The following conclusions are warranted in view of the data reported in Studies I-IV (cf. Sections 5.4.1-5.4.6).

(1) Adult neo-T_3+T_4 rats show a permanently elevated behavioral activity in all tests employed in the present investigation. This is shown as (a) a higher rate of ambulation and rearing behavior, (b) faster exit and running times and (c) shorter total and escape-latencies.

(2) Two explanations of the high rate of behavioral activity have been supported (a) there is an elevated responsiveness to novel stimuli, at least among female neo-T_3+T_4 rats, (b) neo-T_3+T_4 rats habituate their behavioral activity slower than normal rats.

(3) In an effort to investigate the cross-situational character of learning deficits in neo-T_3+T_4 rats, tests of differing "complexity" were used. Although the definition of "complexity" was rudimentary, a certain amount of support was obtained for the proposition that neo-T_3+T_4 rats perform better than controls on "simple" tests, equal on "intermediate" tests, and worse on "complex" tests and test phases. Assessments of test "complexity" must, in this case, contain a judgement of the compatibility/incompatibility of behavioral hyperactivity with efficient learning of the task at hand. Thus, the proposition that neo-T_3+T_4-treatment results in a deficiency of "general learning ability" cannot be supported from

the present data.

(4) Enriched pre-weaning conditions were shown to reduce hyperactivity and speed up the slow rate of habituation in neo-T_3+T_4 rats, although the results were not entirely consistent. Performance improvements in "simple" test, and initial perseverative responding in "complex" test phases could likewise be reversed by pre-weaning enriched rearing. Post-weaning enriched conditions revealed, rather than reversed, behavioral hyperactivity in neo-T_3+T_4 rats, and performance deficits in "complex" test phases were more deficient in neo-T_3+T_4 rats after pre- and post-weaning enrichment.

(5) Thus, pre- and post-weaning enriched rearing conditions are not equally effective in alleviating hyperactivity and learning changes in neo-T_3+T_4 rats. The proposed explanation of this phenomenon is that neo-T_3+T_4 rats are more responsive to pre-weaning enrichment than normal rats, and less responsive to post-weaning enrichment.

(6) A model by Schapiro (1968, 1971a) is supported by the present data. This model states that the neo-T_3 T_4 rats show learning deficits as adults, since they have been prevented from profiting optimally from their rearing environment. This is brought about by neonatal thyroid hormone-treatment, which speeds up the rate of CNS-development during the pre-weaning period. The model is extended to neo-T_3+T_4 rats, behavioral activity and performance improvements on "simple" learning tasks, and is further modified on two points: (a) neo-T_3+T_4 rats are better able to profit from pre-weaning rearing conditions, provided that these are sufficiently varied and stimulating, (b) neo-T_3+T_4 rats are less able to profit from post-weaning rearing conditions, even when enriched, since their CNSs show several phenomena of a detrimental effect of neonatal thyroid hormone-treatment during this period.

of virtually all of these cases, I have come to the conclusion that there are certain aspects of the early (birth to 6 months) and later (3-9 years) signs of NGD that are of particular interest for the present work.

There seems to be a relatively unanimous opinion among clinicians that the following symptoms are present in the newborn NGD case: premature delivery and/or low birth weight, an insatiable appetite, an accelerated bone age, behavioral hyperactivity with hyper-reactive reflexes and premature craniosynostosis (closure of the skull sutures). All or some these signs have been reported in several works (Duggan, Keener & Gay, 1970; Menking, Wiebel, Schmid, Schmidt, Ebel & Ritter, 1972; Robinson, Hall & Munro, 1969). Also, an advancement of neurological development for approximately two months has been observed (Farrehi, 1968). Several of these symptoms are known to occur in association with thyroid hyperactivity, and must be considered as direct effects of an elevated level of thyroid hormones. It is obvious that several of these symptoms are very similar to those reviewed above with regard to the administration of thyroid hormones to newborn rodents (Section 2.1).

Long-term follow-up has been virtually neglected by clinicians and researchers reporting on NGD. Thus, I have been able to locate only eight reports where at least rudimentary follow-up has been performed (Altman, 1950; Givner, Bruger & Lowenstein, 1947; Hollingsworth, Mabry & Eckerd, 1972; Hollingsworth & Mabry, 1975, 1976; Keynes & Litt, 1952; Wilroy & Etteldorf, 1971; Riggs, Wilroy & Etteldorf, 1972). Among these, only two groups of researchers have been concerned with aspects of interest for the present work (Hollingsworth & Mabry, 1975, 1976; Riggs, Wilroy & Etteldorf, 1972). The syndrome that emerges from these few reports on long-term follow-ups of NGD cases is growth retardation, behavioral hyperactivity, mental retardation, and perceptuo-motor problems in children aged 5-9 years. These phenomena persist in the reported cases in spite of an euthyroid state. It may be worthwhile to quote Hollingsworth and Mabry's (1976) impressionistic description of these children:

> "they are extremely active and quick. They flit within moments from one distraction to another; their moods are volatile and they range from joy to tears or angry hostility within seconds. They can, however focus on a task and quickly master complex routines or mechanical skills. Their quickness is a bit deceiving and they appear even brighter and more intelligent than their IQs would indicate" (p. 171).

In spite of the fact that (1) only a small number of cases has been studied (8) with respect to these variables around age 5 - 9 years and (2) the determination of their intellectual status and behavioral activity leaves a lot to be desired, there are strong indications that they

have many problems in common with the neo-T_3+T_4 rat, as reviewed above. In fact, the similarities are so great that I would like to propose that the neo-T_3+T_4 rat can serve as a preliminary model for neonatal Graves' Disease.

In any case, the data reported for the neo-T_3/T_4- and neo-T_3+T_4- animals, and the data provided by Hollingsworth and Mabry (1975, 1976) do prompt a need for long-term investigations of mental and emotional development and status of NGD children. Also, these data point to the necessity of an extreme caution with regard to thyroid medication of neonatally hypothyroid children (see e.g. Penfold & Simpson, 1975) and, also, with regard to both thyroid and anti-thyroid medication of pregnant mothers (cf. Fisher & Burrow, 1975, pp. 113-116). Thus, not only can we agree with Penfold and Simpson (1975) who stated that

> "there seems to be no justification for recommending that it is better to 'err on the side of overtreatment (with respect to T_4-medication to hypothyroid children) in hope of improving cerebral function'" (p. 363).

Rather, there seems to be definite risks involved in administering too high T_4-doses during the early childhood in view of the data from animal experiments.

6.2. Animal models

McKinney and Bunney (1969; McKinney, 1974), in an effort to develop an animal model for human depression, have proposed five criteria against which animal models of human problems can be evaluated (McKinney & Bunney, 1969, p. 246). An adaptation of these criteria for the purpose of the present thesis yields the following: (1) The symptoms of the animal disorder should be reasonably analogous to those seen in the human disorder; (2) There should be observable behavioral changes which can be objectively evaluated; (3) Independent observers should agree on objective criteria for drawing conclusions about any subjective state accompanying the human disorder; (4) The treatments effective in reversing the human disorder should also reverse the animal disorder, and (5) The animal model should be reproducible by other investigators. For the data on the neonatally hyperthyroid rat to be accepted as a model for, primarily NGD in humans, and secondarily as a model for the so-called hyperkinetic syndrome in children, at least some of these criteria should be fulfilled. As of today, criteria 1, 2, and 5 can be said to be reasonably matched by the model for NGD. Problems associated with criterion 3 have not yet been approached and criterion 4 still needs to be explored. However, for

the latter problem, data have been reviewed (Section 5), showing that additional environmental stimulation during an early postnatal period may be successful in reversing some of the behavioral and learning symptoms associated with NGD (Studies II-IV; Davenport, 1976). As for the hyperkinetic syndrome, the same reasoning applies, although the degree of fulfillment of the criteria is lower than for NGD. However, as to criterion 4, we have recently observed, in so-far unpublished studies, that administration of relatively high doses of amphetamine to adult neo-T_3+T_4 rats, results in a considerable reduction of their behavioral activity in at least two separate types of activity tests. This finding is similar to the well-known lowering of behavioral activity in hyperkinetic children after the administration of CNS-stimulants (e.g. Krippner, Silverman, Cavallo & Healy, 1973). By proposing the neonatally hyperthyroid rat as a model for childhood hyperkinesis it is not suggested that this problem results from an excessive early thyroid hormone stimulation. However, this cause of the hyperkinetic syndrome should not be overlooked. In order for the proposed model to be accepted as valid for hyperkinesis, far more work to satisfy criterion 1 must be carried out.

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